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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

1300 I STREET, N.W.  
WASHINGTON, DC 20005-3315

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**Box Patent Application  
Assistant Commissioner for Patents  
Washington, D.C. 20231**

New U.S. Patent Application

Title: STREPTOGRAMINES, THEIR PREPARATION AND COMPOSITIONS  
CONTAINING THEM

being a Continuation of PCT International Application No. PCT/FR98/01639,  
filed July 24, 1998.

Inventor: Alain COMMERÇON  
Address: Vitry-Sur-Seine, France

Inventor: Hervé BOUCHARD  
Address: Thiais, France

Inventor: Yves RIBEILL  
Address: Raleigh, North Carolina, U.S.A.

Inventor: Eric BACQUE  
Address: Morsang Sur Orge, France

Inventor: Baptiste RONAN  
Address: Clamart, France

Inventor: Jean-Claude BARRIERE  
Address: Bures Sur YVETTE, France

Inventor: Gérard PUCHAULT  
Address: Marcilly, France

Inventor: Corinne TERRIER  
Address: Livry GARGAN, France

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.  
Assistant Commissioner for Patents  
January 27, 2000  
Page 2

Sir:

We enclose the following papers for filing in the United States Patent and Trademark Office under 35 U.S.C. 111(a) as a Continuation application of PCT International Application No. PCT/FR98/01639, filed July 24, 1998, which claimed priority of French Application No. 97/09,557 filed July 28, 1997.

1. A check for \$1,004.00 representing the filing fee.
2. Preliminary Amendment.
3. Application - 80 pages, including 1 independent claim, 23 claims total (as amended).
4. Certified copy of French Application No. 97/09,557 filed July 28, 1997.

This application is being filed under the provisions of 37 C.F.R. § 1.53(f).  
Applicants await notification from the Patent and Trademark Office of the time set for filing the Declaration.

Applicants claim the right to priority based on French Application No. 97/09,557 filed July 28, 1997.

Please accord this application a serial number and filing date.

The Commissioner is hereby authorized to charge any additional filing fees due and any other fees due under 37 C.F.R. § 1.16 or § 1.17 during the pendency of this application to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

By:

  
Ernest F. Chapman  
Reg. No. 25,961

EFC/FPD/rgm  
Enclosures

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Alain COMMERCON et al. )  
Serial No.: To be assigned ) Group Art Unit: Unassigned  
Filed: January 27, 2000 ) Examiner: Unassigned

For: STREPTOGRAMINES, THEIR PREPARATION AND COMPOSITIONS  
CONTAINING THEM  
being a Continuation of PCT International Application No. PCT/FR98/01639,  
filed July 24, 1998.

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

**PRELIMINARY AMENDMENT**

Prior to the examination of the above application, please amend this application  
as follows:

**IN THE SPECIFICATION:**

Please amend the specification as follows:

Page 1, before line 3, insert --This application is a continuation of International  
Application No. PCT/FR98/01639, filed July 24, 1998, the content of which is  
incorporated herein by reference--.

**IN THE CLAIMS:**

In claim 3, line 2, please delete "or 2".

Attorney Docket No. 3806.0464-00

If there is any fee due in connection with the filing of this Preliminary  
Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

By: Carol P. Einaudi

Carol P. Einaudi  
Reg. No. 32,220

January 27, 2000

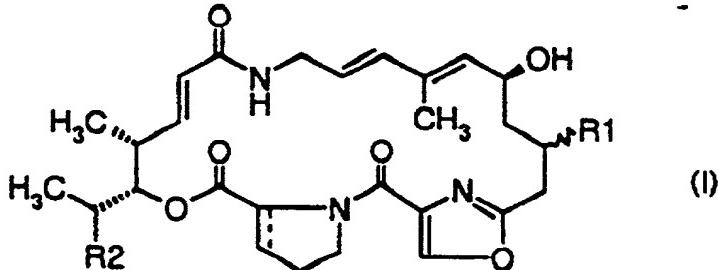
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FINNEGAN, HENDERSON,  
FARABOW, GARRETT,  
& DUNNER, L.L.P.  
1300 I STREET, N.W.  
WASHINGTON, D.C. 20005  
202-408-4000

STREPTOGRAMIN DERIVATIVES, THEIR PREPARATION  
AND COMPOSITIONS CONTAINING THEM

The present invention relates to group A streptogramin derivatives of general formula:



5

in which

- $R_1$  is a radical  $-NR'R''$  for which  $R'$  is a hydrogen atom or a methyl radical, and  $R''$  is a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl, benzyl or  $-OR'''$  radical,  $R'''$  being a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl or benzyl radical, or  $R''$  represents  $-NR_3R_4$ , it being possible for  $R_3$  and  $R_4$  to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur,
- $R_2$  is a hydrogen atom or a methyl or ethyl radical, and

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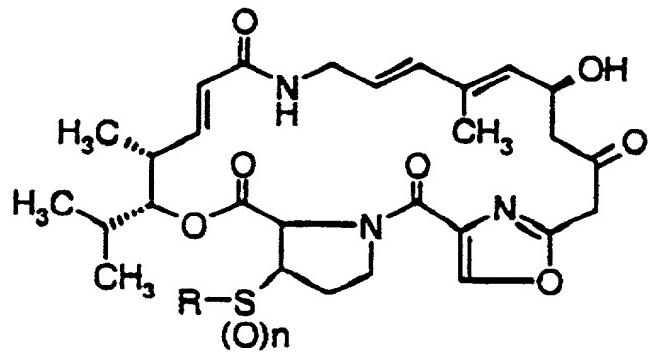
- the bond --- represents a single bond or a double bond,

as well as their salts, which exhibit a particularly  
 5 advantageous antibacterial activity and a good degree  
 of metabolic stability.

Among the known streptogramins, pristinamycin (RP 7293), an antibacterial of natural origin produced by *Streptomyces pristinaespiralis* was first isolated in  
 10 1955. The pristinamycin marketed under the name Pyrostacine<sup>7</sup> consists mainly of pristinamycin II<sub>A</sub> combined with pristinamycin I<sub>A</sub>.

Another antibacterial of the class of streptogramins: virginiamycin, has been prepared from  
 15 *Streptomyces virginiae*, ATCC 13161 [Antibiotics and Chemotherapy, 5, 632 (1955)]. Virginiamycin (Staphylomycine<sup>7</sup>) consists mainly of factor M<sub>1</sub> combined with factor S.

Semisynthetic derivatives of streptogramins  
 20 of structure:

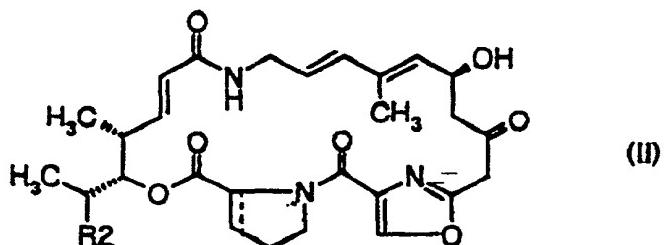


for which n is 0 to 2 have been described in patents EP 135410 and EP 191662. Combined with a semisynthetic component of group B streptogramins they manifest a synergistic action and can be used by the injection route.

In general formula (I), unless otherwise stated, the alkyl radicals are straight or branched and contain 1 to 6 carbon atoms; the cycloalkyl radicals contain 3 to 4 carbon atoms; the chain ~~wavy~~ at the 16-position means: when R'' is other than -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R and S epimers and mixtures thereof.

When R'' is a radical -NR<sub>3</sub>R<sub>4</sub> for which R<sub>3</sub> and R<sub>4</sub> form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle, the latter may be in particular azetidine, azolidine or imidazolyl.

The streptogramin derivatives of general formula (I) may be prepared from the components of the natural pristinamycin of general formula:



in which R<sub>2</sub> is as defined above, by the action of an

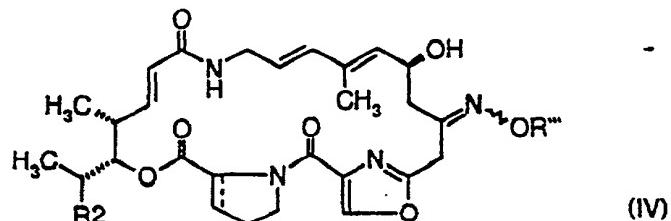
amine of general formula:



in which  $\text{R}''$  is as defined above, followed by the action of an agent for reducing the intermediate  
5 enamine (or oxime) obtained, and then, when it is desired to obtain a streptogramin derivative of general formula (I) for which  $\text{R}'$  is a methyl radical, followed by a second reductive amination, by the action of formaldehyde or of a derivative generating formaldehyde  
10 in situ and the reduction of the intermediate enamine.

The action of the amine is generally carried out in an organic solvent such as an alcohol (for example methanol or ethanol), a chlorinated solvent (for example dichloromethane, dichloroethane or  
15 chloroform), a nitrile (for example acetonitrile), or pyridine, at a temperature of between 0 and 30°C, and optionally in the presence of a dehydrating agent such as, for example, magnesium sulphate, sodium sulphate or molecular sieves. Preferably, the procedure is carried  
20 out under an inert atmosphere (for example argon). It is also possible to cause the amine salt to react. Preferably, to prepare derivatives for which the bond  
--- represents a double bond, the procedure is carried out in an organic solvent such as a nitrile (for  
25 example acetonitrile) in the presence of an acid, such as an organic acid (for example acetic acid); in this case, the addition of a dehydrating agent is not necessary. When a streptogramin derivative of general

formula (I) for which R'' is a radical -OR''' is prepared, it is possible to isolate the intermediate oxime of general formula:



5

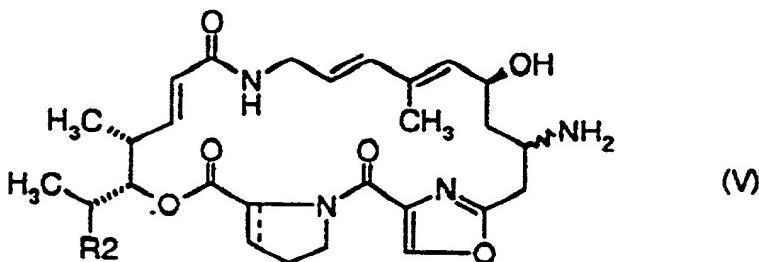
in which R<sub>2</sub> and R''' are as defined above, and then to reduce this product to a derivative of general formula (I) for which R' is a hydrogen atom, and optionally use 10 it in the subsequent reductive amination operation.

The reduction is carried out by the action of a reducing agent, for example an alkali metal borohydride (for example sodium cyanoborohydride or triacetoxyborohydride) in the presence of an organic acid (for example acetic acid) in an organic solvent as 15 mentioned above for the amination reaction.

Where appropriate, the subsequent reductive amination operation, intended to obtain the disubstituted amine, is carried out under similar 20 conditions.

According to the invention, the streptogramin derivatives of general formula (I) may also be prepared by the action of the ketone corresponding to the desired R'' radical on the amine-containing derivative

of general formula:



- 5 in which  $R_2$  is as defined above, followed, when it is  
 desired to obtain a streptogramin derivative of general  
 formula (I) for which  $R'$  is a methyl radical, by a  
 second reductive amination, by the action of  
 formaldehyde or of a derivative generating formaldehyde  
 10 in situ and the reduction of the intermediate enamine.

The reaction is carried out under conditions  
 similar to those described above.

- 15 The amine of general formula (I) may be  
 prepared as described above, from a streptogramin  
 derivative of general formula (II).

The pristinamycin derivatives of general  
 formula (II) correspond respectively to pristinamycin  
 $II_A$  ( $PII_A$ ), to pristinamycin  $II_B$  ( $PII_B$ ), to pristinamycin  
 $II_C$  ( $PII_C$ ), to pristinamycin  $II_D$  ( $PII_D$ ), to pristinamycin  
 20  $II_F$  ( $PII_F$ ), and to pristinamycin  $II_G$  ( $PII_G$ ), which are  
 known components of natural pristinamycin. The  
 components  $PII_F$  and  $PII_G$  have been described in European  
 patent application EP 614910.

Pristinamycin  $II_C$  ( $PII_C$ ) and pristinamycin  $II_D$

( $\text{PII}_D$ ) may be obtained as described by J.C. Barrière et al., Expert. Opin. Invest. Drugs, 3(2), 115-31 (1994).

The preparation and separation of the components of the natural group A streptogramins

5 [streptogramins of general formula (II)] is carried out by fermentation and isolation of the constituents from the fermentation broth according to or by analogy with the method described by J. Preud'homme et al., Bull. Soc. Chim. Fr., vol. 2, 585 (1968).

10 Alternatively, the preparation of the natural components of group A may be carried out by specific fermentation, as described in patent application FR 2,689,518.

15 The streptogramin derivatives of general formula (I) may be purified, where appropriate, by physical methods such as crystallization or chromatography.

The derivatives of general formula (I) may in particular be obtained in the form of the 16R epimer.

20 The separation of the 16R epimer form and the 16S epimer form may be carried out by flash chromatography, by high-performance liquid chromatography (HPLC) or by centrifugal partition chromatography (CPC), from the mixture of the 16R and 16S epimers.

25 The streptogramin derivatives of general formula (I) may be converted to the state of addition salts with acids, by known methods. It is understood that these salts are also included within the scope of

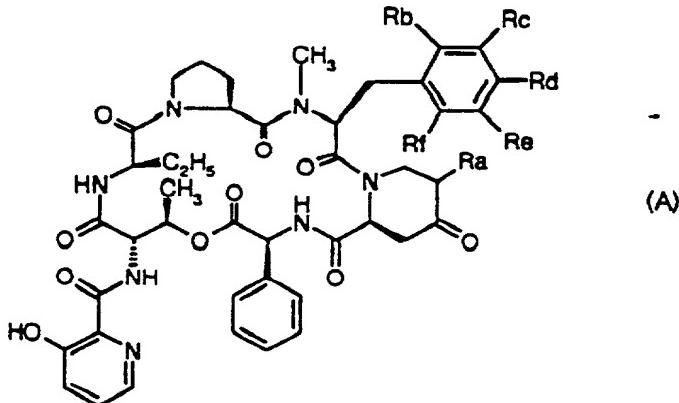
the present invention.

As examples of addition salts with pharmaceutically acceptable acids, there may be mentioned the salts formed with inorganic acids (hydrochlorides, hydrobromides, sulphates, nitrates, sulphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulphonates, ethanesulphonates, phenylsulphonates, p-toluenesulphonates, isethionates, naphthylsulphonates or camphorsulphonates, or with the substitution derivatives of these compounds).

The streptogramin derivatives according to the present invention have antibacterial properties and properties synergizing the antibacterial activity of the group B streptogramin derivatives. They are particularly advantageous because of their activity, alone or combined, as well as because of their enhanced metabolic stability compared with the previously known group A derivatives.

When they are combined with a component or a derivative of the group B streptogramins, they may be chosen, depending on whether it is desired to obtain an orally or parenterally administrable form, from the natural components: pristinamycin I<sub>A</sub>, pristinamycin I<sub>B</sub>, pristinamycin I<sub>C</sub>, pristinamycin I<sub>D</sub>, pristinamycin I<sub>E</sub>, pristinamycin I<sub>F</sub>, pristinamycin I<sub>G</sub>, virginiamycin S<sub>1</sub>, S<sub>3</sub> or S<sub>4</sub>, vernamycin B or C, etamycin or from the semisynthetic derivatives as described in patents or

patent applications US 4,618,599, US 4,798,827,  
US 5,326,782, EP 772630 or EP 770132, in particular the  
streptogramin derivatives of general formula:



5

in which,

1. Rb, Rc, Re and Rf are hydrogen atoms, Rd is a hydrogen atom or a dimethylamino radical, and Ra is a radical of structure  $-\text{CH}_2\text{R}'\text{a}$  for which R'a is 3-pyrrolidinylthio or 3- or 4-piperidylthio which may be substituted with alkyl, or alkylthio substituted with 1 or 2 hydroxysulphonyl, alkylamino, dialkylamino (itself optionally substituted with mercapto or dialkylamino), or
- 10 15 substituted with 1 or 2 optionally substituted piperazine rings, morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or 3-pyrrolidinyl (which may be substituted with alkyl), or alternatively Ra is a radical of structure  $=\text{CHR}'\text{a}$  for which R'a is
- 20 3-pyrrolidinylamino, 3- or 4-piperidylamino,

- 3-pyrrolidinyloxy, 3- or 4-piperidyloxy,  
3-pyrrolidinylthio, 3- or 4-piperidylthio which  
may be substituted with alkyl, or R'a is  
alkylamino, alkyloxy or alkylthio substituted with  
5 1 or 2 hydroxysulphonyl, alkylamino, dialkylamino  
(itself optionally substituted with dialkylamino),  
or with trialkylammonio, 4- or 5-imidazolyl, or  
with 1 or 2 optionally substituted piperazine  
rings, morpholino, thiomorpholino, piperidino,  
10 1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or  
3-pyrrolidinyl (which may be substituted with  
alkyl), or  
Ra is a 3- or 4-quinuclidinylthiomethyl radical,  
or alternatively  
15 2. Ra is a hydrogen atom and  
  
a) either Rb, Re and Rf are hydrogen atoms, Rd is a  
radical -NHCH<sub>3</sub> or -N(CH<sub>3</sub>)<sub>2</sub> and Rc is a chlorine or  
bromine atom, or represents an alkenyl radical  
20 containing 3 to 5 carbon atoms [if Rd is -N(CH<sub>3</sub>)<sub>2</sub>],  
  
b) or Rb, Rd, Re and Rf represent a hydrogen atom and  
Rc is a halogen, or an aminomonooalkyl,  
aminodialkyl, alkyloxy, trifluoromethoxy,  
25 thioalkyl, C<sub>1</sub> to C<sub>3</sub> alkyl or trihalomethyl radical,  
  
c) or Rb, Rc, Re and Rf represent a hydrogen atom and  
Rd is a halogen, or an ethylamino, diethylamino or

methylethylamino, alkyloxy or trifluoromethyloxy, thioalkyl, C<sub>1</sub> to C<sub>6</sub> alkyl, aryl or trihalomethyl radical,

- 5 d) or Rb, Re and Rf represent a hydrogen atom and Rc is halogen or an aminomonooalkyl or aminodialkyl, alkyloxy or trifluoromethyloxy, thioalkyl or C<sub>1</sub> to C<sub>3</sub> alkyl radical, and Rd is halogen or an amino, aminomonooalkyl or aminodialkyl, alkyloxy or trifluoromethyloxy, thioalkyl, C<sub>1</sub> to C<sub>6</sub> alkyl or trihalomethyl radical,
- 10 e) or Rc, Re and Rf represent a hydrogen atom and Rb and Rd represent a methyl radical.

15

It is understood that the combinations of the derivatives according to the invention and of the group B streptogramins are also included within the scope of the present invention.

20 In vivo, on experimental infections of mice with *Staphylococcus aureus* IP 8203 at doses of between 25 and 150 mg/kg orally and/or subcutaneously (CD<sub>50</sub>), they synergize the antimicrobial activity of pristinamycin I<sub>B</sub> of prostinamycin I<sub>A</sub> or of quinupristin 25 (30/70 combination).

Finally, the products according to the invention are particularly advantageous because of their low toxicity. None of the products exhibited

toxicity at doses of 300 mg/kg or greater than 300 mg/kg by the subcutaneous route.

Of particular interest are the products of general formula (I) for which R<sub>1</sub> is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl, cycloalkyl, allyl, propynyl, benzyl or -OR''' radical, R''' being an alkyl radical containing 1 to 6 carbon atoms, an allyl or propynyl radical, or R'' represents -NR<sub>3</sub>R<sub>4</sub>, it being possible for R<sub>3</sub> and R<sub>4</sub> to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur, R<sub>2</sub> is a hydrogen atom or a methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts and in which the chain ~~-----~~ at the 16-position means: when R'' is other than -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R and S epimers and mixtures thereof; and among these products, most particularly the derivatives of general formula (I) for which R<sub>1</sub> is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, a cycloalkyl, allyl, propynyl, benzyl or -OR''' radical, R''' being an alkyl radical containing 1 to 3 carbon atoms.

atoms, or an allyl or propynyl radical, or R'' represents -NR<sub>3</sub>R<sub>4</sub>, it being possible for R<sub>3</sub> and R<sub>4</sub> to form together with the nitrogen atom to which they are attached a 5-membered saturated heterocycle, R<sub>2</sub> is a 5 methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts and in which the chain at the 16-position is as defined above.

More especially, among these products, the 10 following derivatives are of great interest:

- (16R)-16-dimethylamino-16-deoxopristinamycin II<sub>A</sub>;
- (16R)-16-methoxyamino-16-deoxopristinamycin II<sub>B</sub>;
- (16R)-16-ethoxyamino-16-deoxopristinamycin II<sub>B</sub>;
- (16R)-16-allyloxyamino-16-deoxopristinamycin II<sub>B</sub>;
- 15 • (16R)-16-methoxyamino-16-deoxopristinamycin II<sub>A</sub>.

The following examples, given with no limitation being applied, illustrate the present invention.

In the examples which follow, the 20 16-deoxopristinamycin II<sub>A</sub> (or II<sub>B</sub>) nomenclature means the replacement of the ketone function at the 16-position with 2 hydrogen atoms.

Example 1

(16R)-16-Benzylamino-16-deoxopristinamycin II<sub>B</sub>

25 3 g of magnesium sulphate and 0.328 cm<sup>3</sup> of benzylamine are added at about 20EC, under an argon atmosphere, to 1.06 g of pristinamycin II<sub>B</sub> in solution in 15 cm<sup>3</sup> of methanol. After stirring for 24 hours,

0.151 g of sodium cyanoborohydride and 0.5 cm<sup>3</sup> of acetic acid are added. The reaction mixture is stirred for 1 hour and then filtered on Celite. The Celite is washed with 100 cm<sup>3</sup> of methanol, the filtrate is concentrated under reduced pressure (2.7 kPa) to give a residue which is diluted in 200 cm<sup>3</sup> of dichloromethane. The organic phase is washed with twice 100 cm<sup>3</sup> of a 5% aqueous sodium hydrogen carbonate solution. The organic phase is decanted off and the aqueous phase is taken up in twice 50 cm<sup>3</sup> of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give 1.3 g of a residue which is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (84-8-8 by volume)]. 0.424 g of a mixture of the (16R)/(16S) isomers = 65/35 of 16-benzylamino-16-deoxopristinamycin II<sub>B</sub>, in the form of a yellow powder, and 0.144 g of the mixture of the (16R)/(16S) isomers > 95/5 of 16-benzylamino-16-deoxopristinamycin II<sub>B</sub>, in the form of a yellow powder, are thus obtained. Each of these mixtures is purified by HPLC [C18 column (15-20 µm), ( $\lambda$  = 254 nm), eluent: acetonitrile-water (80-20 by volume)] to give, in total, 0.250 g of (16R)-16-benzylamino-16-deoxopristinamycin II<sub>B</sub> in the form of a pale yellow powder melting at around 130EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>,  $\delta$  in ppm): 0.95 and

1.00 (2 d,  $J = 6.5$  Hz, 3H each :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position 31) ; 1.08 (d,  $J = 6.5$  Hz, 3H :  $\text{CH}_3$  at position 32) ; 1.43 (mt, 1H : 1H of  $\text{CH}_2$  at position 15) ; 1.68 (s, 3H :  $\text{CH}_3$  at position 33) ; from 1.70 to 5 2.00 (mt, 5H : 1H of  $\text{CH}_2$  at position 15 -  $\text{CH}_2$  at position 25 - 1H of  $\text{CH}_2$  at position 26 and CH at position 29) ; 2.12 (mt, 1H : 1H of  $\text{CH}_2$  at position 26) ; from 2.65 to 2.80 (mt, 1H : CH at position 4) ; 2.78 and 3.18 (2 dd, respectively  $J = 16$  and 8 Hz and 10  $J = 16$  and 4 Hz, 1H each :  $\text{CH}_2$  at position 17) ; 3.25 (mt, 1H : CH at position 16) ; 3.47 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; 3.80 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; 3.81 and 4.02 (2 d,  $J = 14$  Hz, 1H each :  $\text{CH}_2\text{N}$ ) ; 3.96 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; 4.38 (mt, 15 1H : 1H of  $\text{CH}_2$  at position 9) ; 4.66 (mt, 1H : CH at position 14) ; from 4.70 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 5.36 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 5.64 (mt, 1H : CH at position 10) ; 5.78 (dd,  $J = 16$  and 2 Hz, 1H : CH at position 20) ; 6.00 (mt, 1H : CONH) ; 6.14 (d,  $J = 16$  Hz, 1H : CH at position 11) ; 6.50 (dd,  $J = 16$  and 5 Hz, 1H : CH at position 5) ; from 7.25 to 7.40 (mt, 5H ; aromatic H of benzyl) ; 8.09 (s, 1H : CH at position 20).

Example 2  
25 (16R)-16-Cyclopropylamino-16-deoxopristinamycin II<sub>B</sub>  
9 g of magnesium sulphate and 0.6 cm<sup>3</sup> of cyclopropylamine are added at about 20EC, under an argon atmosphere, to 3 g of pristinamycin II<sub>B</sub> in

solution in 30 cm<sup>3</sup> of methanol. After stirring for  
17 hours 30 minutes, 0.43 g of sodium cyanoborohydride  
is added and then, after 30 minutes, 0.5 cm<sup>3</sup> of acetic  
acid. The reaction mixture is stirred for 2 hours and  
5 then filtered on Celite. The Celite is washed with  
methanol and then the filtrate is concentrated under  
reduced pressure (2.7 kPa) to give 4.64 g of a yellow  
foam which is dissolved in 100 cm<sup>3</sup> of ethyl acetate and  
5 cm<sup>3</sup> of methanol and then washed with 3 times 25 cm<sup>3</sup> of  
10 distilled water. The organic phases are combined, dried  
over magnesium sulphate, filtered and then concentrated  
under reduced pressure (2.7 kPa) to give 2.2 g of a  
yellow foam which is purified by flash chromatography  
[eluent: dichloromethane-methanol-acetonitrile (84-8-8  
15 by volume)]. 0.61 g of a yellow powder is isolated  
which is stirred in 15 cm<sup>3</sup> of ethyl ether, filtered and  
then dried under reduced pressure (2.7 kPa), at 30EC,  
to give 0.508 g of (16R)-16-cyclopropylamino-16-  
deoxopristinamycin II<sub>B</sub> in the form of a cream-coloured  
20 powder melting at around 135EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.35 to 0.60  
(mt, 4H : CH<sub>2</sub> of cyclopropyl) ; 0.97 and 1.00 (2 d, J =  
6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at  
25 position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position  
32) ; 1.33 (mt, 1H : 1H of CH<sub>2</sub> at position 15) ; from  
1.70 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position 15 - CH<sub>2</sub> at  
position 25 - 1H of CH<sub>2</sub> at position 26 and CH at

position 29); 1.77 (s, 3H : CH<sub>3</sub> at position 33) ; 2.13  
(mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 2.29 (mt, 1H : CH  
of cyclopropyl) ; 2.74 (mt, 1H : CH at position 4) ;  
2.82 and 3.25 (2 dd, respectively J = 16 and 8 Hz and J  
5 = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; 3.33 (mt,  
1H : CH at position 16) ; 3.51 (mt, 1H : 1H of CH<sub>2</sub> at  
position 9) ; 3.83 and 3.99 (2 mts, 1H each : CH<sub>2</sub> at  
position 24) ; 4.35 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ;  
4.65 (mt, 1H : CH at position 14) ; from 4.70 to 4.80  
10 (mt, 2H : CH at position 3 and CH at position 27) ;  
5.39 (d, J = 9 Hz, 1H : CH at position 13) ; 5.65 (mt,  
1H : CH at position 10) ; 5.79 (dd, J = 17 and 2 Hz, 1H  
: CH at position 6) ; 5.97 (mt, 1H : CONH) ; 6.17 (d, J  
= 16 Hz, 1H : CH at position 11) ; 6.53 (dd, J = 17 and  
15 5 Hz, 1H : CH at position 5) ; 8.12 (s, 1H : CH at  
position 20).

Example 3

(16R)-16-Allylamino-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure in a manner  
20 similar to that described in Example 1, but starting  
with 5 g of pristinamycin II<sub>B</sub> in solution in 70 cm<sup>3</sup> of  
methanol, 15 g of magnesium sulphate and 1.45 cm<sup>3</sup> of  
allylamine and after adding at 24 hours [lacuna] 0.714  
g of sodium cyanoborohydride and 5 cm<sup>3</sup> of acetic acid, a  
25 solid is obtained after stirring for a further 1 hour  
and after treatment, which solid is purified by flash  
chromatography [eluent: dichloromethane-methanol (95-5  
by volume)] to give 0.975 g of (16R)-16-allylamino-16-

deoxopristinamycin II<sub>B</sub> in the form of a pale yellow powder melting at around 122-124EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.96 and  
5 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and  
CH<sub>3</sub> at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at  
position 32) ; 1.38 (mt, 1H : 1H of CH<sub>2</sub> at position  
15) ; from 1.65 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position  
15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and  
10 CH at position 29) ; 1.77 (s, 3H : CH<sub>3</sub> at position 33) ;  
2.12 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; from 2.70 to  
2.80 (mt, 1H : CH at position 4) ; 2.74 and 3.13 (2 dd,  
respectively J = 16 and 8 Hz and J = 16 and 5 Hz, 1H  
each : CH<sub>2</sub> at position 17); from 3.20 to 3.35 (mt, 2H :  
15 CH at position 16 and 1H of CH<sub>2</sub>N) ; from 3.45 to 3.55  
(mt, 2H : 1H of CH<sub>2</sub> at position 9 and 1H of CH<sub>2</sub>N) ; 3.83  
and 3.98 (2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.38  
(mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 4.70 (mt, 1H : CH  
at position 14); from 4.65 to 4.80 (mt, 2H : CH at  
20 position 3 and CH at position 27) ; 5.15 and 5.24 (2  
dd, respectively J = 10 and 1.5 Hz and J = 18 and 1.5  
Hz, 1H each : =CH<sub>2</sub> of allyl) ; 5.40 (d, J = 9 Hz, 1H :  
CH at position 13); 5.66 (mt, 1H : CH at position 10) ;  
5.80 (dd, J = 17 and 2.5 Hz, 1H : CH at position 6) ;  
25 from 5.85 to 6.00 (mt, 2H : CH= of allyl and CONH) ;  
6.16 (d, J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd,  
J = 17 and 5 Hz, 1H : CH at position 5) ; 8.10 (s, 1H :  
CH at position 20).

Example 4

(16R)-16-Propyn-2-ylamino-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure in a manner similar to that described in Example 1, but starting 5 with 5 g of pristinamycin II<sub>B</sub> in solution in 70 cm<sup>3</sup> of methanol, 10 g of magnesium sulphate and 1.3 cm<sup>3</sup> of propargylamine and after adding at 22 hours [lacuna] 0.714 g of sodium cyanoborohydride and 5 cm<sup>3</sup> of acetic acid, 5.5 g of a solid are obtained after stirring for 10 a further 3 hours 30 min and after treatment, which solid is purified by flash chromatography [eluent: dichloromethane-methanol (96-4 by volume)] to [lacuna] 0.266 g of (16R)-16-propyn-2-ylamino-16-deoxopristinamycin II<sub>B</sub> in the form of an ochre-coloured 15 powder melting at around 124EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at 20 position 32) ; 1.53 (mt, 1H : 1H of CH<sub>2</sub> at position 15) ; from 1.60 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.79 (s, 3H : CH<sub>3</sub> at position 33) ; 2.13 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 2.26 (t, J = 25 2 Hz, 1H : CH propynyl) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.76 and 3.16 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; 3.36 (mt, 1H : CH at position 16) ; 3.48

(mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 3.56 (limiting AB,  
2H : NCH<sub>2</sub> propynyl) ; 3.84 and 3.99 (2 mts, 1H each :  
CH<sub>2</sub> at position 24) ; 4.40 (mt, 1H : 1H of CH<sub>2</sub> at  
position 9) ; from 4.65 to 4.80 (mt, 3H : CH at  
5 position 3 - CH at position 14 and CH at position 27) ;  
5.36 (d, J = 9 Hz, 1H : CH at position 13); 5.69 (mt,  
1H : CH at position 10) ; 5.80 (dd, J = 16 and 2 Hz, 1H  
: CH at position 6) ; 6.11 (mt, 1H : CONH) ; 6.17 (d, J  
= 16 Hz, 1H : CH at position 11) ; 6.52 (dd, J = 16 and  
10 5 Hz, 1H : CH at position 5) ; 8.08 (s, 1H : CH at  
position 20).

Example 5

(16R)-16-[ (R) -sec-Butylamino]-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure in a manner  
15 similar to that described in Example 1, but starting  
with 5 g of pristinamycin II<sub>B</sub> in solution in 70 cm<sup>3</sup> of  
methanol, 10 g of magnesium sulphate and 1.92 cm<sup>3</sup> of  
(R)-sec-butylamine and after adding at 20 hours of  
stirring 0.714 g of sodium cyanoborohydride and 5 cm<sup>3</sup> of  
20 acetic acid, 5.6 g of a solid are obtained after  
stirring for a further 2 hours 30 min and after  
treatment, which solid is purified by flash  
chromatography [eluent: dichloromethane-methanol (96-4  
by volume)] to give 0.680 g of (16R)-16-[ (R) -sec-  
butylamino]-16-deoxopristinamycin II<sub>B</sub> in the form of a  
25 yellow powder melting at around 156EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm) : from 0.90 to

1.15 (mt, 15H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31  
- CH<sub>3</sub> at position 32 and 2 CH<sub>3</sub> of (N-2-butyl)) ; 1.28  
(mt, 2H : CH<sub>2</sub> of (N-1-methylpropyl)) ; 1.50 to 2.20 (mt,  
7H : CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - CH<sub>2</sub> at  
5 position 26 and CH at position 29); 1.79 (s, 3H : CH<sub>3</sub> at  
position 33) ; 2.74 (mt, 1H : CH at position 4) ; from  
3.00 to 3.10 (mt, 2H : CH of (N-1-methylpropyl) and 1H  
of CH<sub>2</sub> at position 17) ; 3.25 (dd, J = 16 and 4 Hz, 1H :  
1H of CH<sub>2</sub> at position 17) ; from 3.50 to 3.60 (mt, 2H :  
10 1H of CH<sub>2</sub> at position 9 and CH at position 16) ; 3.80  
and 3.95 (2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.28  
(mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.70 to 4.85  
(mt, 3H : CH at position 3 - CH at position 4 and CH at  
position 27) ; 5.41 (d, J = 9 Hz, 1H : CH at position  
15 13) ; 5.68 (mt, 1H : CH at position 10) ; 5.80 (d, J =  
16 Hz, 1H : CH at position 6) ; from 6.10 to 6.25  
(broad unresolved complex, 1H : CONH) ; 6.18 (d, J = 16  
Hz, 1H : CH at position 11) ; 6.55 (dd, J = 17 and 5  
Hz, 1H : CH at position 5) ; 8.11 (s, 1H : CH at  
20 position 20).

Example 6

(16R)-16-[(S)-sec-Butylamino]-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure in a manner  
similar to that described in Example 1, but starting  
25 with 5 g of pristinamycin II<sub>B</sub> in solution in 70 cm<sup>3</sup> of  
methanol, 10 g of magnesium sulphate and 1.92 cm<sup>3</sup> of  
(S)-sec-butylamine and by adding after stirring for  
20 hours 0.714 g of sodium cyanoborohydride and 5 cm<sup>3</sup> of

acetic acid. The reaction mixture is stirred for 2 hours 30 min and gives, after treatment, a solid which is purified by flash chromatography [eluent: dichloromethane-methanol (96-4 by volume)]. The solid obtained is recrystallized from hot acetonitrile to give 0.590 g of (16R)-16-[(S)-sec-butylamino]-16-deoxopristinamycin II<sub>B</sub> in the form of a yellow powder melting at around 150EC (dec.).

10     <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.09 to 1.15 (mt, 15H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 - CH<sub>3</sub> at position 32 and 2 CH<sub>3</sub> of (N-1-methylpropyl)) ; 1.44 (quintuplet, J = 7 Hz, 2H : CH<sub>2</sub> of (N-1-methylpropyl)) ; 1.60 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.76 (s, 3H : CH<sub>3</sub> at position 33) ; 2.04 (broad d, J = 14 Hz, 1H : 1H of CH<sub>2</sub> at position 15) ; 2.11 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; from 2.65 to 2.85 (mt, 1H : CH at position 4) ; 2.70 and 3.12 (2 dd, respectively J = 16 and 11 Hz and J = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; 2.80 (mt, 1H : CH of (N-1-methylpropyl)) ; 3.35 (mt, 1H : CH at position 16) ; 3.50 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 3.81 and 3.98 (2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.33 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and CH at position 27) ; 5.43 (d, J = 9 Hz, 1H : CH at position 13) ; 5.62 (mt, 1H : CH at position 10) ; 5.78

(dd,  $J = 16$  and  $2$  Hz,  $1\text{H}$  : CH at position 6) ;  $5.86$  (mt,  $1\text{H}$  : CONH) ;  $6.17$  (d,  $J = 16$  Hz,  $1\text{H}$  : CH at position 11) ;  $6.53$  (dd,  $J = 17$  and  $5$  Hz,  $1\text{H}$  : CH at position 5);  $8.12$  (s,  $1\text{H}$  : CH at position 20).

5 Example 7

16-Amino-16-deoxopristinamycin II<sub>B</sub>

[mixture of the (16R)/(16S) isomers = 75/25]:

200 g of magnesium sulphate, 74 g of ammonium acetate and 28 g of sodium cyanoborohydride are added  
10 at about 20EC, under an argon atmosphere, to 100 g of pristinamycin II<sub>B</sub> in solution in  $1400 \text{ cm}^3$  of methanol. After stirring for 20 hours, the reaction mixture is filtered on Celite, and then the Celite rinsed with methanol. The filtrate is concentrated under reduced pressure (2.7 kPa) to give a chestnut-coloured oil  
15 which is divided into two equal fractions which are each diluted in  $1000 \text{ cm}^3$  of dichloromethane and then treated with a 5% aqueous sodium bicarbonate solution. The organic phases are decanted off and the aqueous  
20 phases extracted with  $1000 \text{ cm}^3$  of dichloromethane. The organic phases are combined, washed with a saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give 97.5 g of a  
25 dark yellow powder. The latter is purified by flash chromatography [eluent: dichloromethane-methanol (70-30 by volume)] to give 21.7 g of 16-amino-16-deoxopristinamycin II<sub>B</sub> (mixture of the (16R)/(16S)

isomers = 75/25) in the form of a beige-yellow powder.

<sup>1</sup>H NMR spectrum [syn (16R) isomer 75% anti (16S) isomer 25%] (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.94 and 0.98 (2d, J = 5 Hz : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31 of the syn isomer) ; from 0.90 to 1.15 (mt : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> at position 32 of the anti isomer) ; 1.07 (d, J = 6.5 Hz : CH<sub>3</sub> at position 32 of the syn isomer) ; 1.46 (mt : 1H of CH<sub>2</sub> at 10 position 15 of the syn isomer) ; from 1.65 to 2.00 (mt : 1H of CH<sub>2</sub> at position 15 of the syn isomer - 1H of CH<sub>2</sub> at position 15 of the anti isomer - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.73 and 1.78 (2 s : respectively CH<sub>3</sub> at position 33 of the 15 anti isomer and CH<sub>3</sub> at position 33 of the syn isomer) ; from 2.00 to 2.30 (mt : 1H of CH<sub>2</sub> at position 15 of the anti isomer and 1H of CH<sub>2</sub> at position 26) ; from 2.65 to 2.80 (mt : CH at position 4 and 1H of CH<sub>2</sub> at position 17 of the syn isomer) ; from 2.80 to 2.90 (mt : CH<sub>2</sub> at 20 position 17 of the anti isomer) ; 2.95 (dd, J = 16 and 5 Hz : 1H of CH<sub>2</sub> at position 17 of the syn isomer) ; from 3.30 to 3.45 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer and CH at position 16 of the syn isomer) ; 3.48 (mt : 1H of CH<sub>2</sub> at position 9 of the syn isomer) ; 25 3.63 (mt : CH at position 16 of the anti isomer) ; 3.80 and 3.91 (2 mts : respectively CH<sub>2</sub> at position 24 of the anti isomer and CH<sub>2</sub> at position 24 of the syn isomer) ; 4.37 (mt : 1H of CH<sub>2</sub> at position 9 of the syn isomer) ;

4.45 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer) ;  
from 4.65 to 4.80 (mt : CH at position 3 - CH at  
position 27 and CH at position 14 of the syn isomer) ;  
4.85 (mt : CH at position 14 of the anti isomer) ; 5.40  
5 (d, J = 9 Hz : CH at position 13 of the syn isomer) ;  
5.65 (mt : CH at position 10) ; from 5.70 to 5.85 (mt :  
CH at position 6 and CH at position 13 of the anti  
isomer) ; from 6.00 to 6.15 (mt : CONH) ; 6.18 and 6.22  
(2 d, J = 16 Hz, respectively CH at position 11 of the  
10 syn isomer and CH at position 11 of the anti isomer) ;  
6.45 and 6.52 (2 dd, J = 16 and 5 Hz : respectively CH  
at position 5 of the anti isomer and CH at position 5  
of the syn isomer) ; 8.09 and 8.10 (s : respectively CH  
at position 20 of the syn isomer and CH at position 20  
15 of the anti isomer).

Upon high-performance liquid chromatography  
starting with 16-amino-16-deoxopristinamycin II<sub>B</sub>  
(mixture of the (16R)/(16S) isomers = 75/25), (16R)-16-  
amino-16-deoxopristinamycin II<sub>B</sub> is obtained in the form  
20 of a white powder melting at around 130EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and  
0.99 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and  
CH<sub>3</sub> at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at  
25 position 32) ; 1.45 (mt, 1H : 1H of CH<sub>2</sub> at position  
15) ; from 1.65 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position  
15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and  
CH at position 29) ; 1.79 (s, 3H : CH<sub>3</sub> at position 33);

2.12 (mt, 1H : 1H of CH<sub>2</sub> at position 26); from 2.70 to  
2.80 (mt, 1H : CH at position 4) ; 2.76 and 2.98 (2 dd,  
respectively J = 16 and 8 Hz and J = 16 and 5 Hz, 1H  
each : CH<sub>2</sub> at position 17) ; 3.42 (mt, 1H : CH at  
position 16) ; 3.48 (mt, 1H : 1H of CH<sub>2</sub> at position 9);  
3.93 (mt, 2H : CH<sub>2</sub> at position 24) ; 4.40 (mt, 1H : 1H  
of CH<sub>2</sub> at position 9); from 4.70 to 4.80 (mt, 3H : CH at  
position 3 - CH at position 14 and CH at position 27) ;  
5.42 (d, J = 9 Hz, 1H : CH at position 13) ; 5.67 (mt,  
1H : CH at position 10) ; 5.79 (dd, J = 17 and 2.5 Hz,  
1H : CH at position 6) ; 5.93 (mt, 1H : CONH); 6.18 (d,  
J = 16 Hz, 1H : CH at position 11) ; 6.52 (dd, J = 17  
and 5 Hz, 1H : CH at position 5) ; 8.12 (s, 1H : CH at  
position 20).

15   Example 8

16-Methylamino-16-deoxopristinamycin II<sub>B</sub>

[mixture of the (16R)/(16S) isomers = 70/30]:

56 g of magnesium sulphate and 9.46 cm<sup>3</sup> of  
methylamine in solution in ethanol (about 8 M) are  
20 added at about 20EC, under an argon atmosphere, to 20 g  
of pristinamycin II<sub>B</sub> in solution in 280 cm<sup>3</sup> of methanol.  
The reaction mixture is stirred at about 20EC for  
24 hours. The reaction mixture is then filtered on  
Celite, and then the Celite washed several times with  
25 methanol. 2.86 g of sodium cyanoborohydride and 9.46 cm<sup>3</sup>  
of acetic acid are then added to the filtrate. After  
stirring the reaction mixture for 5 hours, the solution  
obtained is concentrated to dryness under reduced

pressure (2.7 kPa) at 30EC. The residue is dissolved in 200 cm<sup>3</sup> of dichloromethane and then washed with a saturated aqueous sodium bicarbonate solution. The aqueous phases are decanted off and then extracted with 5 3H100 cm<sup>3</sup> of dichloromethane. The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2.7 kPa) to give 17.8 g of an orange-coloured powder which is purified by flash chromatography [eluent: 10 dichloromethane-methanol (70-30 then 60/40 by volume)]. 10.5 g of 16-methylamino-16-deoxopristinamycin II<sub>B</sub> (mixture of the (16R)/(16S) isomers = 70/30 are thus isolated in the form of a yellow powder.

15 <sup>1</sup>H NMR spectrum [syn (16R) isomer 70%, anti (16S) isomer 30%] (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> at position 32) ; from 1.20 to 1.40 (mt : 1H of CH<sub>2</sub> at position 15 of the syn isomer) ; from 1.65 to 2.00 (mt 20 : 1H of CH<sub>2</sub> at position 15 of the syn isomer - 1H of CH<sub>2</sub> at position 15 of the anti isomer - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.73 and 1.77 (2 s : respectively CH<sub>3</sub> at position 33 of the anti isomer and CH<sub>3</sub> at position 33 of the syn isomer) ; 25 from 2.05 to 2.15 (mt : 1H of CH<sub>2</sub> at position 26) ; 2.18 (dt, J = 15 and 3 Hz, 1H of CH<sub>2</sub> at position 15 of the anti isomer) ; from 2.20 to 2.60 (broad unresolved complex : NH) ; 2.51 and 2.52 (2 s : respectively NCH<sub>3</sub>

of the anti isomer and  $\text{NCH}_3$  of the syn isomer) ; 2.60  
(dd,  $J = 16$  and 11 Hz : 1H of  $\text{CH}_2$  at position 17 of the  
anti isomer) ; from 2.70 to 2.80 (mt : CH at position  
4) ; 2.75 (dd,  $J = 16$  and 8 Hz : 1H of  $\text{CH}_2$  at position  
5 17 of the syn isomer); from 3.05 to 3.20 (mt : 1H of  $\text{CH}_2$   
at position 17 and CH at position 16 of the syn isomer)  
; from 3.30 to 3.40 (mt : 1H of  $\text{CH}_2$  at position 9 of the  
anti isomer and CH at position 16 of the anti isomer) ;  
3.48 (mt : 1H of  $\text{CH}_2$  at position 9 of the syn isomer) ;  
10 3.83 and 3.98 (2 mts, 2 hours in total :  $\text{CH}_2$  at position  
24) ; 4.37 (mt : 1H of  $\text{CH}_2$  at position 9 of the syn  
isomer) ; 4.50 (mt : 1H of  $\text{CH}_2$  at position 9 of the anti  
isomer) ; from 4.65 to 4.80 (mt : CH at position 3 - CH  
at position 27 and CH at position 14 of the syn isomer)  
15 ; 4.83 (mt : CH at position 14 of the anti isomer) ;  
5.39 (d,  $J = 9$  Hz : CH at position 13 of the syn  
isomer) ; 5.65 (mt, 1H : CH at position 10) ; from 5.70  
to 5.85 (mt : CH at position 6 and CH at position 13 of  
the anti isomer) ; 5.96 (mt, 1H : CONH) ; 6.16 and 6.23  
20 (2 d,  $J = 16$  Hz, 1H in total : respectively CH at  
position 11 of the syn isomer and CH at position 11 of  
the anti isomer) ; 6.45 and 6.52 (2 dd,  $J = 16$  and 5  
Hz, 1H in total : respectively CH at position 5 of the  
anti isomer and CH at position 5 of the syn isomer) ;  
25 8.10 and 8.12 (s : respectively CH at position 20 of  
the syn isomer and CH at position 20 of the anti  
isomer).

Upon high-performance liquid chromatography

starting with 16-methylamino-16-deoxopristinamycin II<sub>B</sub> (mixture of (16R)/(16S) isomers = 70/30), (16R)-16-methylamino-16-deoxopristinamycin II<sub>B</sub> is obtained in the form of a yellow solid melting at around 128EC (dec.).

5      <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.96 and  
1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and  
CH<sub>3</sub> at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at  
position 32) ; 1.33 (mt, 1H : 1H of CH<sub>2</sub> at position  
15) ; from 1.60 to 2.05 (mt, 5H : 1H of CH<sub>2</sub> at position  
10 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and  
CH at position 29) ; 1.75 (s, 3H : CH<sub>3</sub> at position 33) ;  
2.11 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 2.53 (s, 3H :  
NCH<sub>3</sub>) ; 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.75  
and 3.12 (2 dd, respectively J = 16 and 8 Hz and J = 16  
15 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; 3.10 to 3.20  
(mt, 1H : CH at position 16) ; 3.48 (mt, 1H : 1H of CH<sub>2</sub>  
at position 9) ; 3.82 and 3.98 (2 mts, 1H each : CH<sub>2</sub> at  
position 24) ; 4.37 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ;  
from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at  
20 position 14 and CH at position 27) ; 5.40 (d, J = 9 Hz,  
1H : CH at position 13) ; 5.64 (mt, 1H : CH at position  
10) ; 5.78 (dd, J = 17 and 2.5 Hz, 1H : CH at position  
6) ; 5.96 (mt, 1H : CONH) ; 6.16 (d, J = 16 Hz, 1H : CH  
at position 11) ; 6.52 (dd, J = 17 and 5 Hz, 1H : CH at  
25 position 5) ; 8.10 (s, 1H : CH at position 20).

Example 9

(16R)-16-Isopropylamino-16-deoxopristinamycin II<sub>B</sub>  
hydrochloride

- 72 g of magnesium sulphate, 8.8 g of ammonium acetate and 3.3 g of sodium cyanoborohydride are added at about 20EC, under an argon atmosphere, to 12 g of pristinamycin II<sub>B</sub> in solution in 120 cm<sup>3</sup> of methanol.
- 5 After stirring for 20 hours, 33.5 cm<sup>3</sup> of acetone are added and the reaction mixture is stirred for 7 hours at about 20EC before filtering on Celite. The Celite is washed several times with dichloromethane and the pooled filtrates are concentrated to dryness under reduced pressure (2.7 kPa) at 30EC. The residue is
- 10 dissolved in 400 cm<sup>3</sup> of dichloromethane and the solution thus obtained is washed with 3H200 cm<sup>3</sup> of a saturated aqueous sodium bicarbonate solution. The final organic phase is concentrated to dryness under reduced pressure
- 15 (2.7 kPa) at 30EC to give 11.3 g of an orange-coloured powder which is purified by flash chromatography [gradient elution: n-butanol-ethyl acetate-ethanol-water (10-60-15-15 then 20-50-15-15 then 30-40-15-15 by volume)] to give 2.92 g of 16-isopropylamino-16-
- 20 deoxopristinamycin II<sub>B</sub> (mixture of the (16R)/(16S) isomers = 75/25) in the form of a yellow powder. The two epimers are separated by centrifugal partition chromatography [eluent: ethyl acetate-hexane-methanol-water (2-1-1-1.8 by volume)] to give 0.77 g of (16R)-
- 25 16-isopropylamino-16-deoxopristinamycin II<sub>B</sub> in the form of a white powder. The latter is dissolved in a mixture of 10.8 cm<sup>3</sup> of 0.1N hydrochloric acid and 27.7 cm<sup>3</sup> of water. The solution thus obtained is then filtered and

the filtrate freeze-dried to give 0.72 g of (16R)-16-isopropylamino-16-deoxopristinamycin II<sub>B</sub> hydrochloride in the form of a white powder melting at around 135EC (dec.).

- 5      <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 32) ; 1.44 and 1.54 (2 d, J = 6.5 Hz, 3H each : 2 CH<sub>3</sub> of isopropyl) ; from 1.70 to 2.25 (mt, 7H : CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - CH<sub>2</sub> at position 26 and CH at position 29) ; 1.85 (s, 3H : CH<sub>3</sub> at position 33) ; 2.74 (mt, 1H : CH at position 4) ; 3.34 (mt, 2H : CH<sub>2</sub> at position 17); 3.45 (mt, 1H : CH of isopropyl); 3.56 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 3.67 (mt, 1H : CH at position 16) ; 3.82 and 3.95 (2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.31 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.70 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 4.85 (mt, 1H : CH at position 14) ; 5.41 (d, J = 9 Hz, 1H : CH at position 13) ; 5.75 (mt, 1H : CH at position 10) ; 5.83 (dd, J = 16 and 2 Hz, 1H : CH at position 6) ; 6.22 (d, J = 16 Hz, 1H : CH at position 11) ; 6.46 (mt, 1H : CONH) ; 6.54 (dd, J = 16 and 5 Hz, 1H : CH at position 5); 8.10 (s : CH at position 20).
- 25      Example 10

(16R)-16-Dimethylamino-16-deoxopristinamycin II<sub>B</sub>

50 g of magnesium sulphate and 9.5 cm<sup>3</sup> of methylamine are added at about 20EC, under an argon

atmosphere, to 20 g of pristinamycin II<sub>B</sub> in solution in 300 cm<sup>3</sup> of methanol. After stirring for 22 hours, the reaction mixture is cooled to -5EC and 16.1 g of sodium triacetoxyborohydride are added. The reaction mixture  
5 is stirred for 5 hours between -5EC and 0EC and the temperature is allowed to return to about 20EC over 12 hours. 11.35 g of paraformaldehyde are then added, and then after stirring for 6 hours, 16.1 g of sodium triacetoxyborohydride. The mixture is then stirred for  
10 1 hour before adding 2.27 g of paraformaldehyde. After stirring for 16 hours, the reaction mixture is filtered onto Celite. The Celite is washed with 300 cm<sup>3</sup> of methanol, the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) to give a residue which is  
15 diluted in 500 cm<sup>3</sup> of dichloromethane. The organic phase is washed with 600 cm<sup>3</sup> of a 5% aqueous sodium bicarbonate solution. The organic phase is decanted off and the aqueous phase is taken up in twice 500 cm<sup>3</sup> of dichloromethane. The organic phases are combined, dried  
20 over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give 23 g of a chestnut-coloured powder which is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (90-5-5 by volume)]. 3.4 g of (16R)-16-  
25 dimethylamino-16-deoxopristinamycin II<sub>B</sub> are thus obtained in the form of a chestnut-beige powder melting at around 122EC (dec.)

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and

0.98 (2 d,  $J = 6.5$  Hz, 3H each :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position 31) ; 1.07 (d,  $J = 6.5$  Hz, 3H :  $\text{CH}_3$  at position 32) ; from 1.60 to 2.00 (mt, 6H :  $\text{CH}_2$  at position 15 -  $\text{CH}_2$  at position 25 - 1H of  $\text{CH}_2$  at position 5 26 and CH at position 29) ; 1.78 (s, 3H :  $\text{CH}_3$  at position 33) ; 2.11 (mt, 1H : 1H of  $\text{CH}_2$  at position 26) ; 2.36 (s, 6H :  $\text{N}(\text{CH}_3)_2$ ) ; 2.61 (dd,  $J = 16$  and 10 Hz, 1H : 1H of  $\text{CH}_2$  at position 17) ; 2.72 (mt, 1H : CH at position 4) ; 2.98 (dd,  $J = 16$  and 4 Hz, 1H : 1H of  $\text{CH}_2$  at position 10 17) ; 3.21 (mt, 1H : CH at position 16) ; 3.52 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; 3.83 and 3.92 (2 mts, 1H each :  $\text{CH}_2$  at position 24) ; 4.32 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; 4.67 (mt, 1H : CH at position 14) ; 4.74 (dd,  $J = 9$  and 3 Hz, 1H : CH at position 27) ; 15 4.79 (dd,  $J = 10$  and 2 Hz, 1H : CH at position 3) ; 5.35 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 5.65 (mt, 1H : CH at position 10) ; 5.78 (dd,  $J = 16$  and 2 Hz, 1H : CH at position 6) ; 6.07 (mt, 1H : CONH) ; 6.17 (d,  $J = 16$  Hz, 1H : CH at position 11) ; 6.53 (dd,  $J = 16$  and 5 Hz, 1H : CH at position 5) ; 8.06 (s : CH at position 20).

Example 11

(16R)-16-(Allyl)(methyl)amino-16-deoxopristinamycin II<sub>B</sub>

20 g of magnesium sulphate and 2.3 cm<sup>3</sup> of allylamine are added at around 20EC, under a nitrogen atmosphere, to 7 g of pristinamycin II<sub>B</sub> in solution in 100 cm<sup>3</sup> of methanol. After stirring for 21 hours 45 minutes, 0.5 cm<sup>3</sup> of allylamine is added, and then after

4 hours 45 minutes, 1.67 g of sodium cyanoborohydride and then 7 cm<sup>3</sup> of acetic acid. The reaction mixture is stirred for 4 hours 30 minutes before adding a further 100 mg of sodium cyanoborohydride. After stirring for a 5 further 25 hours, 2.39 g of paraformaldehyde are added and the stirring is continued. The same quantity of paraformaldehyde is added three times at half-an-hour intervals and one hour after the last addition, 450 mg of sodium cyanoborohydride, 3.5 cm<sup>3</sup> of acetic acid and 10 again 2.39 g of paraformaldehyde are added. After stirring for 19 hours 30 minutes, the mixture is filtered on Celite and then rinsed with methanol. The filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30EC and the residue obtained is 15 then taken up in 300 cm<sup>3</sup> of methylene chloride and 600 cm<sup>3</sup> of a 5% sodium bicarbonate solution. The aqueous phase is decanted off and then extracted with 200 cm<sup>3</sup> of methylene chloride. The organic phases are pooled, washed with 300 cm<sup>3</sup> of distilled water, dried over 20 magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) to give a solid which is dried under reduced pressure (90 Pa) at 20EC and then purified by flash chromatography [eluent: dichloromethane-methanol (95-5 by volume)]. 1.25 g of 25 (16R)-16-(allyl)(methyl)amino-16-deoxopristinamycin II<sub>B</sub> are obtained in the form of an off-white solid melting at around 124EC (dec.).

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and

0.99 (2 d,  $J = 6.5$  Hz, 3H each :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position 31) ; 1.08 (d,  $J = 6.5$  Hz, 3H :  $\text{CH}_3$  at position 32) ; from 1.65 to 2.00 (mt, 6H :  $\text{CH}_2$  at position 15 -  $\text{CH}_2$  at position 25 - 1H of  $\text{CH}_2$  at position 5 26 and CH at position 29) ; 1.78 (s, 3H :  $\text{CH}_2$  at position 33) ; 2.12 (mt, 1H : 1H of  $\text{CH}_2$  at position 26); 2.32 (s, 3H :  $\text{NCH}_3$ ) ; 2.64 and 2.98 (2 dd, respectively  $J = 16$  and 10 Hz and  $J = 16$  and 4 Hz, 1H each :  $\text{CH}_2$  at position 17) ; 2.73 (mt, 1H : CH at position 4) ; 3.05 and 3.28 (2 dd, respectively  $J = 14$  and 7 Hz and  $J = 14$  and 6 Hz, 1H each :  $\text{CH}_2$  of N(allyl)) ; 3.35 (mt, 1H : CH at position 16) ; 3.52 (mt, 1H : 1H of  $\text{CH}_2$  at position 10) ; 3.84 and 3.93 (2 mts, 1H each :  $\text{CH}_2$  at position 24) ; 4.34 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; 4.67 (mt, 1H : CH at position 14) ; 4.75 (dd,  $J = 9$  and 2.5 Hz, 1H : CH at position 27) ; 4.80 (dd,  $J = 8$  and 1.5 Hz, 1H : CH at position 3) ; 5.19 and 5.23 (respectively d,  $J = 10$  Hz and dd,  $J = 18$  and 1.5 Hz, 1H each :  $=\text{CH}_2$  of allyl) ; 5.36 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 5.67 (mt, 1H : CH at position 10) ; 5.80 (dd,  $J = 17$  and 2.5 Hz, 1H : CH at position 6) ; from 5.80 to 5.95 (mt, 1H :  $\text{CH=}$  of allyl) ; 6.02 (mt, 1H : CONH) ; 6.18 (d,  $J = 16$  Hz, 1H : CH at position 11) ; 6.53 (dd,  $J = 17$  and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H : CH 25 at position 20).

Example 12

16-Propyn-2-ylamino-16-deoxopristinamycin II<sub>A</sub>

[mixture of the (16R)/(16S) isomers = 65/35]

0.130 cm<sup>3</sup> of propargylamine and then 0.053 cm<sup>3</sup>

5 of acetic acid are added at a temperature close to 20EC, under an argon atmosphere, to 0.5 g of pristinamycin II<sub>A</sub> in solution in 70 cm<sup>3</sup> of anhydrous acetonitrile. The mixture is stirred for 18 hours at a temperature close to 20EC and then a further 0.13 cm<sup>3</sup> of 10 propargylamine is added. The mixture is stirred for 4 hours at a temperature of 20EC and is then concentrated under reduced pressure (2.7 kPa) at a temperature close to 30EC until an insoluble material appears. 0.072 g of sodium cyanoborohydride and then 15 1.2 cm<sup>3</sup> of concentrated acetic acid are then added at a temperature close to 20EC, under an argon atmosphere. The mixture is stirred for 1 hour 30 minutes at a temperature close to 20EC. The reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is then taken up in dichloromethane and the organic phase washed twice with a saturated aqueous sodium bicarbonate solution. The aqueous phases are combined and extracted with dichloromethane. The organic phases are combined, dried 20 over magnesium sulphate, filtered on sintered glass and then concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by 25 preparative plate chromatography (Merck silica gel

60 F<sub>254</sub>; thickness = 2 mm, 20H20 cm), eluting with a dichloromethane-methanol-acetonitrile (90-5-5 by volume) mixture to give 0.205 g of 16-propyn-2-ylamino-16-deoxopristinamycin II<sub>A</sub> (mixture of the (16R)/(16S) isomers = 65/35) in the form of a beige powder.

<sup>1</sup>H NMR spectrum [syn (16R) isomer 65% and anti (16S) isomer 35%] (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31 ; from 1.05 to 1.20 (mt, 3H : CH<sub>3</sub> at position 32) ; from 1.50 to 2.10 (mt : CH<sub>2</sub> at position 15 and CH at position 29) ; 1.64 and 1.74 (2 s : respectively CH<sub>3</sub> at position 33 of the anti isomer and CH<sub>3</sub> at position 33 of the syn isomer) ; 2.27 and 2.32 (2 t, J = 2.5 Hz : respectively CH of 2-propynyl of the syn isomer and CH of 2-propynyl of the anti isomer) ; from 2.55 to 2.95 (mt : CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 17 - CH at position 16 of the syn isomer and CH at position 4) ; 3.00 (dd, J = 14 and 2.5 Hz : 1H of CH<sub>2</sub> at position 17 of the syn isomer) ; 3.22 (dd, J = 14 and 2.5 Hz : 1H of CH<sub>2</sub> at position 17 of the anti isomer) ; 3.36 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer) ; from 3.45 to 3.60 (mt: NCH<sub>2</sub> of 2-propynyl and CH at position 16 of the anti isomer); 3.82 (broad d, J = 18 Hz : 1H of CH<sub>2</sub> at position 9 of the syn isomer) ; from 4.10 to 4.60 (mt : CH<sub>2</sub> at position 24 - 1H of CH<sub>2</sub> at position 9 and CH at position 14 of the syn isomer) ; from 4.75 to 4.85 (mt : CH at position 14 of the anti isomer and CH

at position 13 of the syn isomer) ; from 4.90 to 5.00 (mt, 1H : CH at position 3) ; from 5.45 to 5.60 (mt : CH at position 10 of the anti isomer) ; 5.50 (d, J = 8 Hz : CH at position 13 of the anti isomer) ; 5.64 (mt : 5 CH at position 10 of the syn isomer); from 5.80 to 6.10 (mt : CH at position 6 - CH at position 11 and CH at position 26 of the anti isomer) ; 6.13 (t, J = 3 Hz : CH at position 26 of the syn isomer) ; 6.53 (dd, J = 16 and 6 Hz : CH at position 5 of the anti isomer) ; from 10 6.55 to 6.70 (mt : CONH of the anti isomer) ; 6.61 (dd, J = 16 and 7 Hz ; CH at position 5 of the syn isomer) ; 7.48 (mt : CONH of the syn isomer) ; 7.87 and 8.08 (2 s : respectively CH at position 20 of the syn isomer and CH at position 20 of the anti isomer).

15 Example 13

16-Allylamino-16-deoxopristinamycin II<sub>A</sub>

[mixture of the (16R)/(16S) isomers = 65/35]

0.054 cm<sup>3</sup> of acetic acid is added to a suspension of 0.5 g of pristinamycin II<sub>A</sub> in 15 cm<sup>3</sup> of 20 acetonitrile and 0.143 cm<sup>3</sup> of allylamine, kept at a temperature close to 20EC. After one hour at a temperature close to 20EC, 0.072 g of sodium cyanoborohydride and then 1 cm<sup>3</sup> of acetic acid are added successively. After one hour at a temperature close to 25 20EC, 7 cm<sup>3</sup> of water and 15 cm<sup>3</sup> of dichloromethane are added to the reaction mixture. The organic phase is decanted off and then washed with twice 10 cm<sup>3</sup> of a saturated sodium bicarbonate solution. The aqueous

phases are extracted with 10 cm<sup>3</sup> of dichloromethane. The pooled organic phases are dried over magnesium sulphate, filtered and concentrated under reduced pressure (about 2.7 kPa) at a temperature close to 40EC. A bright yellow foam is thus obtained which is purified by preparative thin-layer chromatography: 6 Merck preparative plates, Kieselgel 60 F<sub>254</sub>, 20H20 cm, thickness 2 mm, deposition in solution in dichloromethane, eluting with a dichloromethane-methanol-acetonitrile (80-10-10 by volume) mixture to give 0.179 g of 16-allylamino-16-deoxopristinamycin II<sub>A</sub> (mixture of the (16R)/(16S) isomers=65/35) in the form of a cream-coloured foam.

15      <sup>1</sup>H NMR spectrum [mixture of the (16R)/(16S) isomers = 65/35] (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.95 to 1.05 (mt, 6H : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; from 1.10 to 1.20 (mt, 3H : CH<sub>3</sub> at position 32) ; 1.64 and 1.71 (2 s, 3H in total : respectively CH<sub>3</sub> at 20 position 33 of the anti isomer and CH<sub>3</sub> at position 33 of the syn isomer) ; from 1.70 to 2.10 (mt, 3H : CH<sub>2</sub> in position 15 and CH in position 29) ; from 2.60 to 2.90 (mt : CH<sub>2</sub> at position 25 - 1H from CH<sub>2</sub> at position 17 - CH at position 16 of the syn isomer and CH at position 25) ; 3.06 (broad d, J = 14 Hz : 1H of CH<sub>2</sub> at position 17 of the syn isomer) ; 3.22 (broad d, J = 15 Hz : 1H of CH<sub>2</sub> at position 17 of the anti isomer) ; from 3.30 to 3.55 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer -

NCH<sub>2</sub> of allyl and CH at position 16 of the anti isomer) ; 3.85 (broad d, J = 18 Hz : 1H of CH<sub>2</sub> at position 9 of the syn isomer) ; from 4.10 to 4.60 (mt : CH<sub>2</sub> at position 24 - 1H of CH<sub>2</sub> at position 9 and CH at position 14 of the syn isomer); 4.80 (mt : CH at position 14 of the anti isomer) ; 4.87 (broad d, J = 8 Hz : CH at position 13 of the syn isomer) ; from 4.90 to 5.00 (mt, 1H : CH at position 3) ; from 5.15 to 5.30 (mt : =CH<sub>2</sub> of allyl) ; from 5.45 to 5.60 (mt : CH at position 10 of the anti isomer); 5.55 (d, J = 9 Hz : CH at position 13 of the anti isomer) ; 5.63 (mt : CH at position 10 of the syn isomer) ; from 5.85 to 6.10 (mt : CH at position 6 - CH at position 11 - CH at position 26 of the anti isomer and =CH of allyl) ; 6.14 (broad s : CH at position 26 of the syn isomer) ; from 6.45 to 6.60 (mt : CH at position 5 of the anti isomer and CONH of the anti isomer) ; 6.62 (dd, J = 16 and 7 Hz : CH at position 5 of the syn isomer) ; 7.39 (mt : CONH of the syn isomer) ; 7.88 and 8.07 (2 s : respectively CH at position 20 of the syn isomer and CH at position 20 of the anti isomer).

Example 14

(16R)-16-Dimethylamino-16-deoxopristinamycin II<sub>A</sub>

6.9 cm<sup>3</sup> of methylamine (8 M in ethanol) and 25 then 1.43 cm<sup>3</sup> of acetic acid are added at a temperature close to 20EC, under an argon atmosphere, to 28.5 g of pristinamycin II<sub>A</sub> in solution in 780 cm<sup>3</sup> of anhydrous acetonitrile. The mixture is stirred for 48 hours at a

temperature close to 20EC and then 3.8 g of sodium cyanoborohydride and 12 cm<sup>3</sup> of acetic acid are added under an argon atmosphere. The mixture is stirred for 3 hours at a temperature close to 20EC before a further 5 addition of 11 cm<sup>3</sup> of acetic acid. The reaction mixture is again stirred for 7.5 hours at a temperature close to 20EC. 6 g of paraformaldehyde are then added and the mixture is kept stirred for 17 hours at a temperature close to 20EC. The white suspension obtained is 10 filtered and the filtrate is concentrated under reduced pressure (2.7 kPa) at a temperature close to 30EC. The residual thick oil is then taken up in 800 cm<sup>3</sup> of ethyl acetate and in 300 cm<sup>3</sup> of water. After stirring for about 15 minutes, the pH of the solution obtained is 15 adjusted first to 9 by addition of concentrated sodium hydroxide, and then to 11 by addition of 150 cm<sup>3</sup> of 1 N sodium hydroxide. The mixture obtained is stirred for about one hour before a further addition of 50 cm<sup>3</sup> of 1 N sodium hydroxide and stirring for a further one 20 hour approximately. The resulting mixture is separated after settling out and the organic phase washed with twice with 100 cm<sup>3</sup> of water and then extracted three times with 1 N HCl (1000 cm<sup>3</sup>, 100 cm<sup>3</sup> and 50 cm<sup>3</sup> successively). The pooled acidic aqueous phases are 25 extraced with 200 cm<sup>3</sup> of ether and then alkalinized to pH 10-11 by addition of 23 cm<sup>3</sup> of concentrated sodium hydroxide. The aqueous phase obtained is extracted with twice 300 cm<sup>3</sup> of dichloromethane and the organic phases

are combined, washed with 100 cm<sup>3</sup> of water, dried over magnesium sulphate, filtered on sintered glass and then concentrated to dryness under reduced pressure (2.7 kPa) at a temperature close to 30EC to give a white solid. The latter is stirred in 200 cm<sup>3</sup> of ether and then filtered and dried to constant weight (90 Pa, at about 20EC), to give 20 g of a white powder. The latter is purified by flash chromatography (eluent: dichloromethane-methanol-acetonitrile (92-4-4 then 84-8-8 by volume)] to give 5.2 g of (16R)-16-dimethylamino-16-deoxopristinamycin II<sub>A</sub> in the form of a white solid. 4.5 g of this solid are recrystallized from an acetonitrile-water (18 cm<sup>3</sup>-9 cm<sup>3</sup>) mixture to give, after draining and drying under reduced pressure (90 Pa, at about 20EC), 3.46 g of a white powder melting at around 212EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.05 (mt, 6H : CH<sub>2</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.13 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 32) ; 1.63 (mt, 1H : 1H of CH<sub>2</sub> at position 15) ; 1.73 (s, 3H : CH<sub>3</sub> at position 33) ; from 1.95 to 2.10 (mt, 2H : 1H of CH<sub>2</sub> at position 15 and CH at position 29) ; 2.36 (s, 6H : N(CH<sub>3</sub>)<sub>2</sub>) ; from 2.50 to 2.65 (mt, 2H : 1H of CH<sub>2</sub> at position 17 and CH at position 16) ; from 2.65 to 2.75 (mt, 2H : CH at position 4 and 1H of CH<sub>2</sub> at position 25) ; from 2.80 to 2.95 (mt, 1H : 1H of CH<sub>2</sub> at position 25) ; 2.97 (d, J = 11 Hz, 1H : 1H of CH<sub>2</sub> at position 17) ;

3.79 (broad d,  $J = 18$  Hz, 1H : 1H of  $\text{CH}_2$  at position 9) ;  
4.21 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; from 4.30 to  
4.50 (mt, 3H : 1H of  $\text{CH}_2$  at position 9 - 1H of  $\text{CH}_2$  at  
position 24 and CH at position 14) ; 4.79 (d,  $J = 9$  Hz,  
5 1H : CH at position 13) ; 4.97 (dd,  $J = 10$  and 1.5 Hz,  
1H : CH at position 3) ; 5.64 (mt, 1H : CH at position  
10) ; 5.90 (broad d,  $J = 16$  Hz, 1H : CH at position 11) ;  
6.04 (d,  $J = 16$  Hz, 1H : CH at position 6) ; 6.13 (t,  $J =$   
3 Hz, 1H : CH at position 26) ; 6.62 (dd,  $J = 17$  and 5  
10 Hz, 1H : CH at position 5); 7.51 (mt, 1H : CONH) ; 7.87  
(s : CH at position 20).

Example 15

(16R)-16-Methylamino-16-deoxopristinamycin II<sub>A</sub>

By carrying out the procedure as described in  
15 Examples 12 and 13, starting with pristinamycin II<sub>A</sub>,  
(16R)-16-methylamino-16-deoxopristinamycin II<sub>A</sub> is  
obtained in the form of a cream-coloured foam melting  
at around 130EC (dec.).

20  $^1\text{H}$  NMR spectrum (400 MHz,  $\text{CDCl}_3$ ,  $\delta$  in ppm): from 0.90 to  
1.05 (mt, 6H :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position  
31) ; 1.12 (d,  $J = 6.5$  Hz, 3H :  $\text{CH}_3$  at position 32) ;  
1.72 (s, 3H :  $\text{CH}_3$  at position 33) ; from 1.80 to 2.10  
(mt, 3H :  $\text{CH}_2$  at position 15 and CH at position 29) ;  
25 2.58 (s, 3H :  $\text{NCH}_3$ ) ; from 2.60 to 2.90 (mt, 4H : CH at  
position 4 - 1H of  $\text{CH}_2$  at position 17 and  $\text{CH}_2$  at  
position 25) ; 3.12 (dd,  $J = 14$  and 1.5 Hz, 1H : 1H of  
 $\text{CH}_2$  at position 17) ; from 3.35 to 3.45 (mt, 1H : CH at

position 16) ; 3.86 (broad d,  $J = 18$  Hz, 1H : 1H of  $\text{CH}_2$  at position 9) ; from 4.18 to 4.40 (mt, 3H : 1H of  $\text{CH}_2$  at position 9 and  $\text{CH}_2$  at position 24) ; 4.55 (mt, 1H : CH at position 14) ; 4.89 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 4.93 (dd,  $J = 10$  and 1.5 Hz, 1H : CH at position 3) ; 5.62 (mt, 1H : CH at position 10) ; 5.90 (d,  $J = 16$  Hz, 1H : CH at position 11) ; 6.01 (d,  $J = 16$  Hz, 1H : CH at position 6) ; 6.14 (t,  $J = 3$  Hz, 1H : CH at position 26) ; 6.61 (dd,  $J = 17$  and 5 Hz, 1H : CH at position 5) ; 7.38 (mt, 1H : CONH) ; 7.90 (s, 1H : CH at position 20).

Example 16

16-Benzylamino-16-deoxopristinamycin II<sub>A</sub>

[mixture of the (16R)/(16S) isomers = 50/50]

By carrying out the procedure as described in Examples 12 and 13, starting with pristinamycin II<sub>A</sub>, 16-benzylamino-16-deoxopristinamycin II<sub>A</sub> [mixture of the (16R)/(16S) isomers = 50/50] is obtained in the form of a white powder.

20

<sup>1</sup>H NMR spectrum [syn (16R) isomer 50% and anti (16S) isomer 50%] (400 MHz,  $\text{CDCl}_3$ ,  $\delta$  in ppm) : from 0.95 to 1.05 (mt, 6H :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position 31) ; from 1.05 to 1.20 (mt, 3H :  $\text{CH}_3$  at position 32) ; 1.45 and 1.63 (2 s : respectively  $\text{CH}_3$  at position 33 of the anti isomer and  $\text{CH}_3$  at position 33 of the syn isomer) ; from 1.50 to 2.15 (mt, the 3H corresponding to:  $\text{CH}_2$  at position 15 and CH at position 29) ; from

2.60 to 2.95 (mt : CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 17 of the anti isomer - CH<sub>2</sub> at position 17 of the syn isomer and CH at position 4) ; 3.12 (mt : CH at position 16 of the syn isomer) ; 3.29 (broad d, J = 5 Hz : 1H of CH<sub>2</sub> at position 17 of the anti isomer) ; 3.35 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer) ; 3.47 (mt : CH at position 16 of the anti isomer) ; from 3.80 to 4.10 (mt : 1H of CH<sub>2</sub> at position 9 of the syn isomer and NCH<sub>2</sub> of benzyl) ; from 4.10 to 4.45 (mt : CH<sub>2</sub> at position 24 - 1H of CH<sub>2</sub> at position 9 of the syn isomer and CH at position 14 of the syn isomer) ; 4.54 (mt : 1H of CH<sub>2</sub> at position 9 of the anti isomer) ; from 4.75 to 4.85 (mt : CH at position 14 of the anti isomer and CH at position 13 of the syn isomer) ; from 4.90 to 5.00 (mt, 1H : CH at position 3) ; 5.40 (d, J = 8 Hz : CH at position 13 of the anti isomer) ; from 5.45 to 5.65 (mt, 1H : CH at position 10) ; from 5.80 to 6.05 (mt, 2H at position 6 and CH at position 11) ; 6.08 and 6.14 (2 t, J = 3 Hz, 1H in total : respectively CH at position 26 of the anti isomer and CH at position 26 of the syn isomer) ; from 6.45 to 6.55 (mt : CONH of the anti isomer) ; 6.54 (dd, J = 16 and 6 Hz : CH at position 5 of the anti isomer) ; 6.61 (dd, J = 16 and 7 Hz : CH at position 5 of the syn isomer) ; from 7.25 to 7.45 (mt : 5H of phenyl and CONH of the syn isomer) ; 7.86 and 8.09 (2 s : respectively CH at position 20 of the syn isomer and CH at position 20 of the anti isomer).

Example 17(16R)-16-Methoxyamino-16-deoxopristinamycin II<sub>B</sub>

10 g of pristinamycin II<sub>B</sub> O-methyloxime (70/30 mixture of the Z and E isomers) in solution in 300 cm<sup>3</sup> of methanol and 100 cm<sup>3</sup> of acetic acid are placed in a round-bottomed flask kept under a nitrogen atmosphere.

5 The mixture is cooled to -70EC before adding 10.3 g of sodium cyanoborohydride. The temperature is allowed risen slowly to about 20EC and the reaction mixture is

10 left unstirred for 48 hours. An argon stream is passed for one hour through the solution kept under an aspirating fume cupboard and then the solvents are evaporated off under reduced pressure (2.7 kPa) at 20EC and the residue is taken up in 200 cm<sup>3</sup> of methylene

15 chloride and 100 cm<sup>3</sup> of distilled water. The aqueous phase is alkalized to pH 8 by addition of 30 cm<sup>3</sup> of concentrated NaOH and the mixture is stirred for 30 minutes before being transferred into a separating funnel. The organic phase is decanted off and then

20 washed with twice 100 cm<sup>3</sup> of distilled water. The organic phase is decanted off, dried over magnesium sulphate, filtered and then concentrated under reduced pressure (2.7 kPa) at 20EC to give a colourless oil which is stirred in diethyl ether; the precipitate

25 obtained is filtered. 9.1 g of a white powder are thus obtained, which powder is purified by flash chromatography (eluent: CH<sub>2</sub>Cl<sub>2</sub>-MeOH 97-3 by volume). 1.88 g of (16R)-16-methoxyamino-16-deoxopristinamycin

II<sub>B</sub> are isolated in the form of a white powder melting at 195EC.

<sup>1</sup>H NMR spectrum (600 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and  
5 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and  
CH<sub>3</sub> at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at  
position 32) ; from 1.60 to 2.00 (mt, 6H : CH<sub>2</sub> at  
position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position  
26 and CH at position 29) ; 1.80 (s, 3H : CH<sub>3</sub> at  
10 position 33) ; 2.15 (mt, 1H : 1H of CH<sub>2</sub> at position  
26) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ;  
2.76 and 3.24 (2 dd, respectively J = 16 and 8 Hz and J  
= 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; from 3.45  
15 to 3.55 (mt, 2H : CH at position 16 and 1H of CH<sub>2</sub> at  
position 9) ; 3.60 (s, 3H : OCH<sub>3</sub>) ; 3.92 (mt, 2H : CH<sub>2</sub>  
at position 24) ; 4.43 (mt, 1H : 1H of CH<sub>2</sub> at position  
9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH  
at position 14 and CH at position 27) ; 5.34 (d, J =  
9 Hz, 1H : CH at position 13) ; 5.70 (mt, 1H : CH at  
20 position 10) ; 5.80 (dd, J = 16 and 2 Hz, 1H : CH at  
position 6) ; 6.14 (mt, 1H : CONH) ; 6.18 (d, J =  
16 Hz, 1H : CH at position 11) ; 6.51 (dd, J = 16 and  
5 Hz, 1H : CH at position 5) ; 8.09 (s, 1H : CH at  
position 20).

25 Pristinamycin II<sub>B</sub> O-methyloxime (70/30 mixture  
of the Z and E isomers) may be prepared in the  
following manner:

20 g of pristinamycin II<sub>B</sub> in solution in

800 cm<sup>3</sup> of anhydrous pyridine are placed in a three-necked flask and 4.2 g of methoxyamine hydrochloride are added. After stirring for 21 hours, the pyridine is evaporated off under reduced pressure (2.7 kPa) at 40EC  
5 and then the residue obtained is taken up in 500 cm<sup>3</sup> of methylene chloride and 1 litre of distilled water. The organic phase is decanted off, washed with twice 1 litre of distilled water, dried over sodium sulphate, filtered and then concentrated to dryness under reduced  
10 pressure (2.7 kPa) at 40EC to give a residue which is stirred in 300 cm<sup>3</sup> of diethyl ether. The precipitate is filtered, dried under reduced pressure (90 Pa) and then purified by flash chromatography (eluent CH<sub>2</sub>Cl<sub>2</sub>-MeOH 95-5 by volume). 16.9 g of pristinamycin II<sub>B</sub> O-methyloxime  
15 (70/30 mixture of the Z and E isomers) are thus obtained in the form of a white solid melting at around 198-199EC (dec.) and which is used as it is in subsequent operations.

20 <sup>1</sup>H NMR spectrum (300 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> at position 32) ; 1.73 and 1.74 (2 s, 3H in total : respectively CH<sub>3</sub> at position 33 of the E isomer and CH<sub>3</sub> at position 33 of the Z isomer) ; from 1.75 to  
25 2.35 (mt : CH<sub>2</sub> at position 25 - CH<sub>2</sub> at position 26 - CH at position 29 and 1H of CH<sub>2</sub> at position 15 of the E isomers) ; 2.51 and 2.65 (2 dd, respectively J = 17 and 6 Hz and J = 17 and 5 Hz : CH<sub>2</sub> at position 15 of the Z

isomer) ; from 2.65 to 2.80 (mt, 1H : CH at position 4) ; 3.00 (dd, J = 13 and 6 Hz : 1H of CH<sub>2</sub> at position 15 of the E isomer) ; 3.22 (d, J = 6 Hz : OH of the Z isomer) ; from 3.30 to 3.45 (mt, 1H : 1H of CH<sub>2</sub> at 5 position 9); 3.58 and 3.68 (2 d, J = 15 Hz : CH<sub>2</sub> at position 17 of the E isomer) ; from 3.65 to 3.80 (mt, 1H : 1H of CH<sub>2</sub> at position 24) ; 3.62 and 4.04 (2 d, J = 16.5 Hz : CH<sub>2</sub> at position 17 of the Z isomer) ; 3.92 and 3.94 (2 s, 3H in total : respectively OCH<sub>3</sub> of the Z 10 isomer and OCH<sub>3</sub> of the E isomer) ; from 3.95 to 4.20 (mt, 1H : 1H of CH<sub>2</sub> at position 24) ; 4.35 to 4.55 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.60 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; from 4.80 to 4.90 (mt : CH at position 13 of the E isomer 15 and CH at position 14 of the Z isomer) ; 5.06 (mt : CH at position 14 of the E isomer) ; 5.57 (d, J = 9 Hz : CH at position 13 of the Z isomer) ; from 5.60 to 5.90 (mt, 2H : CH at position 10 and CH at position 6) ; 6.05 and 6.14 (2 d, J = 16 Hz, 1H in total : 20 respectively CH at position 11 of the E isomer and CH at position 11 of the Z isomer) ; 6.28 (mt : CONH of the Z isomer) ; 6.47 (d, J = 16 and 5 Hz, 1H : CH at position 5) ; 7.47 (mt : CONH of the E isomer) ; 7.77 (s : CH at position 20 of the E isomer) ; 8.08 (s : CH 25 at position 20 of the Z isomer).

Example 18(16R)-16-Ethoxyamino-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure as in Example 17, but starting with 1.53 g of pristinamycin II<sub>B</sub>

5 O-ethyloxime (50/50 mixture of the E and Z isomers) in solution in 45 cm<sup>3</sup> of methanol, 15 cm<sup>3</sup> of acetic acid and 1.67 g of sodium cyanoborohydride and after 67 hours of reaction, 1.4 g of a white solid are obtained, which solid is purified by flash chromatography (eluent

10 CH<sub>2</sub>Cl<sub>2</sub>-MeOH 97/3 by volume) to give 360 mg of (16R)-16-ethoxyamino-16-deoxopristinamycin II<sub>B</sub> in the form of a white solid melting at 205EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.96 and

15 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 32) ; 1.19 (t, J = 7 Hz, 3H : CH<sub>3</sub> of ethyl) ; from 1.60 to 2.00 (mt, 6 H : CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at

20 position 29) ; 1.80 (s, 3H : CH<sub>3</sub> at position 33) ; 2.14 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.76 and 3.26 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; from 3.45 to 3.55 (mt, 2H :

25 CH at position 16 and 1H of CH<sub>2</sub> at position 9) ; 3.79 (q, J = 7 Hz, 2H : CH<sub>2</sub> of ethyl) ; 3.93 (mt, 2H : CH<sub>2</sub> at position 24) ; 4.43 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH at

position 14 and CH at position 27) ; 5.34 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd,  $J = 16$  and 2 Hz, 1H : CH at position 6) ; 6.13 (mt, 1H : CONH) ; 6.17 (d,  $J = 16$  Hz, 1H : CH at 5 position 11); 6.51 (dd,  $J = 16$  and 5 Hz, 1H : CH at position 5); 8.08 (s, 1H : CH at position 20).

Pristinamycin II<sub>B</sub> O-ethyloxime (70/30 mixture of the Z and E isomers) may be prepared by carrying out the procedure as in Example 17, but starting with 12 g 10 of pristinamycin II<sub>B</sub>. 2.44 g of O-ethyl hydroxylamine hydrochloride in 400 cm<sup>3</sup> of pyridine. After extraction and stirring in diethyl ether, 11.28 g of pristinamycin II<sub>B</sub> O-ethyloxime (70/30 mixture of the Z and E isomers) are obtained in the form of a light yellow solid 15 melting at around 114EC (dec.) and which is used as it is for subsequent operations.

<sup>1</sup>H NMR spectrum of the 70/30 mixture of the two Z/E isomers (400 MHz, CDCl<sub>3</sub>,  $\delta$  in ppm): from 0.90 to 1.10 20 (mt, 9H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> at position 32) ; from 1.25 to 1.35 (mt, 3H : CH<sub>3</sub> of ethyl) ; 1.70 and 1.75 (2 s, 3H in total : respectively CH<sub>3</sub> at position 33 of the E isomer and CH<sub>3</sub> at position 33 of the Z isomer) ; from 1.75 to 2.35 (mt : CH<sub>2</sub> at 25 position 25 - CH<sub>2</sub> at position 26 - CH at position 29 and 1H of CH<sub>2</sub> at position 15 of the E isomer) ; 2.52 and 2.68 (2 dd, respectively  $J = 16.5$  and 6 Hz and  $J = 16.5$  and 5 Hz : CH<sub>2</sub> at position 15 of the Z isomer) ; from

2.70 to 2.80 (mt, 1H : CH at position 4) ; 3.02 (dd,  
J = 13 and 5 Hz : 1H of  $\text{CH}_2$  at position 15 of the E  
isomer) ; 3.25 (d, J = 6 Hz : OH of the Z isomer) ;  
from 3.30 to 3.45 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ;  
5 3.61 and 3.72 (2 d, J = 15 Hz :  $\text{CH}_2$  at position 17 of  
the E isomer) ; from 3.70 to 3.80 (mt, 1H : 1H of  $\text{CH}_2$  at  
position 24) ; 3.63 and 4.07 (2 d, J = 16 Hz :  $\text{CH}_2$  at  
position 17 of the Z isomer) ; from 4.00 to 4.25 (mt,  
3H : 1H of  $\text{CH}_2$  at position 24 and  $\text{OCH}_2$ ) ; from 4.40 to  
10 4.55 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; from 4.65 to  
4.90 (mt : CH at position 27 - CH at position 3 and CH  
at position 14 of the Z isomer) ; 4.91 (d, J = 9 Hz :  
CH at position 13 of the E isomer) ; 5.08 (mt : CH at  
position 14 of the E isomer) ; 5.59 (d, J = 9 Hz : CH  
15 at position 13 of the Z isomer) ; from 5.65 to 5.80  
(mt, 1H : CH at position 10) ; 5.79 and 5.85 (2 dd,  
respectively J = 17 and 2 Hz and J = 17 and 1.5 Hz, 1H  
in total : CH at position 6 of the Z isomer and CH at  
position 6 of the E isomer) ; 6.06 and 6.15 (2 d, J =  
20 16 Hz, 1H in total : respectively CH at position 11 of  
the E isomer and CH at position 11 of the Z isomer) ;  
6.24 (mt : CONH of the Z isomer) ; from 6.40 to 6.55  
(mt, 1H : CH at position 5) ; 7.43 (mt : CONH of the E  
isomer) ; 7.79 (s : CH at position 20 of the E  
25 isomer) ; 8.09 (s : CH at position 20 of the Z isomer).

Example 19

(16R)-16-Allyloxyamino-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure as in Example 17, but starting with 1.46 g of pristinamycin II<sub>B</sub> 5 O-allyloxime (65/35 mixture of the Z/E isomers) in solution in 42 cm<sup>3</sup> of methanol, 14 cm<sup>3</sup> of acetic acid and 1.57 g of sodium cyanoborohydride and after 96 hours of reaction, 1.3 g of a white solid are isolated, which solid is purified by flash chromatography (eluent 10 (CH<sub>2</sub>Cl<sub>2</sub>-MeOH 97/3 by volume) to give 0.31 g of (16R)-16-allyloxyamino-16-deoxopristinamycin II<sub>B</sub> in the form of a white solid melting at 130EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and 15 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.07 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 32) ; from 1.60 to 2.05 (mt, 6H : CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.80 (s, 3H : CH<sub>3</sub> at 20 position 33) ; 2.14 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 2.24 (broad s, 1H : OH) ; from 2.70 to 2.85 (mt, 1H : CH at position 4) ; 2.77 and 3.27 (2 dd, respectively J = 16 and 8 Hz and J = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; from 3.45 to 3.55 (mt, 2H : 25 CH at position 16 and 1H of CH<sub>2</sub> at position 9); 3.92 (mt, 2H : CH<sub>2</sub> at position 24) ; 4.25 (mt, 2H : CH<sub>2</sub>O) ; 4.43 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; from 4.70 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and

CH at position 27); 5.23 and 5.30 (2 dd, respectively J = 10 and 1.5 Hz and J = 18 and 1.5 Hz, 1H each : =CH<sub>2</sub> of allyl) ; 5.34 (d, J = 9 Hz, 1H : CH at position 13) ; 5.60 (unresolved complex, 1H : NH) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd, J = 16 and 2 Hz, 1H : CH at position 6) ; 5.95 (mt, 1H : CH of allyl) ; 6.12 (mt, 1H : CONH) ; 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.51 (dd, J = 16 and 5 Hz, 1H : CH at position 5) ; 8.09 (s, 1H : CH at position 20).

10                   Pristinamycin II<sub>B</sub> O-allyloxime (65/55 mixture of the Z and E isomers) may be prepared by carrying out the procedure as in Example 17, but starting with 5 g of pristinamycin II<sub>B</sub>, 1.14 g of O-allylhydroxylamine hydrochloride in 200 cm<sup>3</sup> of pyridine. After extraction 15 and stirring in diethyl ether, 4.2 g of pristinamycin II<sub>B</sub> O-allyloxime (65/55 mixture of the Z and E isomers) are obtained in the form of an ochre-coloured solid melting at 102-104EC and which solid is used as it is for subsequent operations.

20                   <sup>1</sup>H NMR spectrum (300 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.10 (mt, 9H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> at position 32) ; 1.73 and 1.74 (2 s, 3H in total : respectively CH<sub>3</sub> at position 33 of the E isomer 25 and CH<sub>3</sub> at position 33 of the Z isomer) ; from 1.75 to 2.35 (mt : CH<sub>2</sub> at position 25 - CH<sub>2</sub> at position 26 - CH at position 29 and 1H of CH<sub>2</sub> at position 15 of the E isomer) ; 2.51 and 2.65 (2 dd, respectively J = 17 and

6 Hz and  $J = 17$  and 5 Hz :  $\text{CH}_2$  at position 15 of the Z isomer) ; from 2.65 to 2.80 (mt, 1H : CH at position 4) ; 3.00 (dd,  $J = 13$  and 6 Hz : 1H of  $\text{CH}_2$  at position 15 of the E isomer) ; 3.22 (d,  $J = 6$  Hz : OH of the Z isomer) ; from 3.30 to 3.45 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; 3.58 and 3.68 (2 d,  $J = 15$  Hz :  $\text{CH}_2$  at position 17 of the E isomer) ; from 3.65 to 3.80 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; 3.62 and 4.04 (2 d,  $J = 16.5$  Hz :  $\text{CH}_2$  at position 17 of the Z isomer) ; 3.92 and 10 3.94 (2 s, 3H in total : respectively  $\text{OCH}_3$  of the Z isomer and  $\text{OCH}_3$  of the E isomer) ; from 3.95 to 4.20 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; from 4.35 to 4.55 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; from 4.60 to 4.80 (mt, 2H : CH at position 3 and CH at position 27) ; 15 from 4.80 to 4.90 (mt : CH at position 13 of the E isomer and CH at position 14 of the Z isomer) ; 5.06 (mt : CH at position 14 of the E isomer) ; 5.57 (d,  $J = 9$  Hz : CH at position 13 of the Z isomer) ; from 5.60 to 5.90 (mt, 2H : CH at position 10 and CH at position 20 6) ; 6.05 and 6.14 (2 d,  $J = 16$  Hz, 1H in total : respectively CH at position 11 of the E isomer and CH at position 11 of the Z isomer) ; 6.28 (mt : CONH of the Z isomer) ; 6.47 (d,  $J = 16$  and 5 Hz, 1H : CH at position 5) ; 7.47 (mt : CONH of the E isomer) ; 7.77 25 (s : CH at position 20 of the E isomer) ; 8.08 (s : CH at position 20 of the Z isomer).

Example 20

(16R)-16-Propyloxyamino-16-deoxopristinamycin II<sub>B</sub>

- By carrying out the procedure as in Example 17, but starting with 1.5 g of pristinamycin II<sub>B</sub>
- 5 O-propyloxime (50/50 mixture of the Z and E isomers) in solution in 45 cm<sup>3</sup> of methanol, 15 cm<sup>3</sup> of acetic acid and 1.61 g of sodium cyanoborohydride and after 50 hours of reaction, 1.4 g of a white solid are isolated, which solid is purified by flash chromatography (eluent CH<sub>2</sub>Cl<sub>2</sub>-MeOH 97/3 by volume) to give 0.31 g of (16R)-16-propyloxyamino-16-deoxopristinamycin II<sub>B</sub> in the form of a white solid melting at 135EC.
- 15 <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.05 (mt, 9H : CH<sub>3</sub> at position 30 - CH<sub>3</sub> at position 31 and CH<sub>3</sub> of propyl) ; 1.08 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 32) ; from 1.55 to 1.70 (mt, 3H : 1H of CH<sub>2</sub> at position 15 and central CH<sub>2</sub> of propyl) ; from 1.70 to 2.00 (mt, 5H : 1H of CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.80 (s, 3H : CH<sub>3</sub> at position 33) ; 2.14 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; from 2.20 to 2.35 (broad unresolved complex, 1H : OH) ; from 2.70 to 2.80 (mt, 1H : CH at position 4) ; 2.75 (dd, J = 16 and 8 Hz, 1H : 1H of CH<sub>2</sub> at position 17) ; 3.27 (dd, J = 16 and 4 Hz, 1H : 1H of CH<sub>2</sub> at position 17) ; from 3.40 to 3.55 (mt, 2H : CH at position 16 and 1H of CH<sub>2</sub> at

position 9) ; 3.69 (t,  $J = 6.5$  Hz, 2H :  $\text{OCH}_2$ ) ; from 3.85 to 4.00 (mt, 2H :  $\text{CH}_2$  at position 24) ; 4.43 (mt, 1H : 1H of  $\text{CH}_2$  at position 9) ; from 4.65 to 4.80 (mt, 3H : CH at position 3 - CH at position 14 and CH at 5 position 27) ; 5.36 (d,  $J = 9$  Hz, 1H : CH at position 13) ; from 5.40 to 5.60 (broad unresolved complex, 1H : NH) ; 5.70 (mt, 1H : CH at position 10) ; 5.80 (dd,  $J = 16$  and 1.5 Hz, 1H : CH at position 6) ; 6.14 (mt, 1H : CONH) ; 6.17 (d,  $J = 16$  Hz, 1H : CH at position 11) ; 10 6.51 (dd,  $J = 16$  and 5 Hz, 1H : CH at position 5) ; 8.08 (s, 1H : CH at position 20).

Pristinamycin II<sub>B</sub> O-propylloxime (85/15 mixture of the Z and E isomers) may be prepared by carrying out the procedure as in Example 17, but starting with 4 g 15 of pristinamycin II<sub>B</sub>, 2.6 g of O-propylhydroxylamine hydrochloride in 60 cm<sup>3</sup> of pyridine. After extraction and drying under reduced pressure (2.7 kPa) at 20EC, a solid is obtained which is stirred in acetonitrile to give, after filtration of the precipitate, 2.75 g of 20 pristinamycin II<sub>B</sub> O-propylloxime (85/15 mixture of the Z and E isomers) in the form of a white solid melting at 130-132EC and which is used as it is for subsequent operations.

25 <sup>1</sup>H NMR spectrum (400 MHz,  $\text{CDCl}_3$ ,  $\delta$  in ppm): from 0.90 to 1.10 (mt, 12H :  $\text{CH}_3$  at position 30 -  $\text{CH}_3$  at position 31 -  $\text{CH}_3$  at position 32 and  $\text{CH}_3$  of propyl) ; from 1.60 to 1.75 (mt, 2H : central  $\text{CH}_2$  of propyl) ; 1.75 (s, 3H :

CH<sub>3</sub> at position 33) ; from 1.75 to 2.00 (mt, 4H : CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 2.15 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 2.51 and 2.65 (2 dd, respectively J = 17 and 6 Hz and J = 17.5 and 5 Hz, 1H each : CH<sub>2</sub> at position 15) ; 2.74 (mt, 1H : CH at position 4); 3.20 (d, J = 6 Hz, 1H : OH) ; 3.38 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 3.65 (d, J = 15 Hz, 1H : 1H of CH<sub>2</sub> at position 17) ; 3.74 (mt, 1H : 1H of CH<sub>2</sub> at position 24) ; from 3.95 to 4.10 (mt, 4H : 1H of CH<sub>2</sub> at position 24 - 1H of CH<sub>2</sub> at position 17 and OCH<sub>2</sub>) ; 4.43 (mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 4.67 (dd, J = 10 and 3 Hz, 1H : CH at position 27) ; 4.72 (broad d, J = 10 Hz, 1H : CH at position 3) ; 4.83 (mt, 1H : CH at position 14) ; 5.55 (d, J = 9 Hz, 1H : CH at position 13) ; 5.69 (mt, 1H : CH at position 10) ; 5.78 (dd, J = 17 and 1.5 Hz, 1H : CH at position 6) ; 6.13 (d, J = 16 Hz, 1H : CH at position 11) ; 6.26 (mt, 1H : CONH) ; 6.46 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H : CH at position 20).

Example 21

(16R)-16-Methoxyamino-16-deoxopristinamycin II<sub>A</sub>

This compound may be obtained by carrying out the procedure as in Example 17, but starting with 3 g of pristinamycin II<sub>A</sub> O-methyloxime (65/25 mixture of the Z and E isomers) in solution in 90 cm<sup>3</sup> of methanol, 30 cm<sup>3</sup> of acetic acid and 3.4 g of sodium cyanoborohydride and after one week of reaction at

about 20EC and one week of reaction at 30-33EC. 3 g of a white solid are thus obtained, which solid is purified by flash chromatography (eluent  $\text{CH}_2\text{Cl}_2$ -MeOH 97/3 by volume) to give 0.36 g of (16R)-16-methoxyamino-16-deoxopristinamycin II<sub>A</sub> in the form of a white solid melting at 150EC.

<sup>1</sup>H NMR spectrum (400 MHz,  $\text{CDCl}_3$ ,  $\delta$  in ppm): from 0.90 to 1.05 (mt, 6H :  $\text{CH}_3$  at position 30 and  $\text{CH}_3$  at position 31) ; 1.13 (d,  $J = 6.5$  Hz, 3H :  $\text{CH}_3$  at position 32) ; 1.59 (broad s, 1H : OH) ; from 1.65 to 1.85 (mt, 2H :  $\text{CH}_2$  at position 15) ; 1.73 (s, 3H :  $\text{CH}_3$  at position 33) ; 2.03 (mt, 1H : CH at position 29) ; from 2.60 to 2.85 (mt, 2H : CH at position 4 and 1H of  $\text{CH}_2$  at position 25) ; 2.64 (dd,  $J = 14$  and 11 Hz, 1H : 1H of  $\text{CH}_2$  at position 17) ; 2.85 (mt, 1H : 1H of  $\text{CH}_2$  at position 25) ; 2.95 (mt, 1H : CH at position 16) ; 3.20 (dd,  $J = 14$  and 2.5 Hz, 1H : 1H of  $\text{CH}_2$  at position 17) ; 3.60 (s, 3H :  $\text{OCH}_3$ ) ; 3.81 (broad d,  $J = 18$  Hz, 1H : 1H of  $\text{CH}_2$  at position 9) ; 4.22 (mt, 1H : 1H of  $\text{CH}_2$  at position 24) ; from 4.30 to 4.55 (mt, 3H : 1H of  $\text{CH}_2$  at position 9 - 1H of  $\text{CH}_2$  at position 24 and CH at position 14) ; 4.83 (d,  $J = 9$  Hz, 1H : CH at position 13) ; 4.96 (broad d,  $J = 10$  Hz, 1H : CH at position 3) ; 5.47 (broad s, 1H : NH) ; 5.65 (mt, 1H : CH at position 10) ; 5.90 (broad d,  $J = 16$  Hz, 1H : CH at position 11) ; 6.03 (broad d,  $J = 17$  Hz, 1H : CH at position 6) ; 6.14 (t,  $J = 3$  Hz, 1H : CH at position 26) ; 6.62 (dd,  $J = 17$  and 7 Hz, 1H : CH

at position 5) ; 7.48 (mt, 1H : CONH) ; 7.87 (s, 1H : CH at position 20).

Pristinamycin II<sub>A</sub> O-methyloxime (65/35 mixture of the Z and E isomers) may be obtained by carrying out  
5 the procedure as in Example 17, but starting with 8 g of pristinamycin II<sub>A</sub> and 1.43 g of methoxyamine hydrochloride in 80 cm<sup>3</sup> of pyridine. After evaporation of the pyridine under reduced pressure (2.7 kPa) at 45EC, extraction, stirring of the product in 300 cm<sup>3</sup> of  
10 diethyl ether, filtration and washing with diethyl ether, 7.51 g of pristinamycin II<sub>A</sub> O-methyloxime (65/35 mixture of the Z and E isomers) are obtained after drying under reduced pressure (90 Pa) at 40EC in the form of a white solid melting at around 204EC and which  
15 is used as it is in subsequent operations.

#### Example 22

(16R)-16-(1-Pyrrolidinyl)amino-16-deoxopristinamycin II<sub>B</sub>

By carrying out the procedure as in Example  
20 17, but starting with 3 g of pristinamycin II<sub>B</sub> in solution in 30 cm<sup>3</sup> of methanol, 9 g of magnesium sulphate, 1.6 cm<sup>3</sup> of triethylamine and 1.4 g of 1-aminopyrrolidine hydrochloride and after having added, after 18 hours of stirring, 0.43 g of sodium  
25 cyanoborohydride and 1.5 cm<sup>3</sup> of acetic acid, the reaction mixture is stirred for 4 hours and gives after treatment 3.5 g of a yellow powder which is purified by flash chromatography [eluent: dichloromethane-methanol-

acetonitrile (90-5-5 by volume)]. A solid is thus obtained which is stirred in ethyl ether and separated by filtration to give 0.56 g of (16R)-16-(1-pyrrolidinyl)amino-16-deoxopristinamycin II<sub>B</sub> in the form  
5 of a beige powder melting at around 130EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): 0.95 and 1.00 (2 d, J = 6.5 Hz, 3H each : CH<sub>3</sub> at position 30 and CH<sub>3</sub> at position 31) ; 1.06 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at 10 position 32) ; 1.53 (mt, 1H : 1H of CH<sub>2</sub> at position 15) ; from 1.70 to 2.20 (mt, 10H : 1H of CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - CH<sub>2</sub> at position 26 - CH at position 29 and 2 CH<sub>2</sub> of pyrrolidinyl) ; 1.83 (s, 3H : CH<sub>3</sub> at position 33) ; from 2.70 to 2.90 (mt, 6H : CH at 15 position 4 - 1H of CH<sub>2</sub> at position 17 and 2 CH<sub>2</sub>N of pyrrolidinyl) ; 3.06 (dd, J = 16 and 4 Hz, 1H : 1H of CH<sub>2</sub> at position 17) ; from 3.40 to 3.50 (mt, 2H : 1H of CH<sub>2</sub> at position 9 and CH at position 16) ; 3.82 and 3.97 (2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.37 (mt, 1H : 20 1H of CH<sub>2</sub> at position 9); 4.57 (mt, 1H : CH at position 14) ; 4.73 (dd, J = 9 and 3 Hz, 1H : CH at position 27) ; 4.77 (dd, J = 10 and 2 Hz, 1H : CH at position 3) ; 5.41 (d, J = 9 Hz, 1H : CH at position 13) ; 5.68 (mt, 1H : CH at position 10) ; 5.78 (dd, J = 17 and 25 2 Hz, 1H : CH at position 6) ; 6.01 (mt, 1H : CONH) ; 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.50 (dd, J = 17 and 5 Hz, 1H : CH at position 5) ; 8.10 (s, 1H : CH at position 20).

Example 23(16R)-16-Dimethylamino-16-deoxypristinamycin II<sub>F</sub>

0.069 cm<sup>3</sup> of methylamine (8 M in ethanol) and then 0.015 cm<sup>3</sup> of acetic acid are added at a temperature close to 20EC, under an argon atmosphere, to 0.27 g of pristinamycin II<sub>F</sub> in solution in 7 cm<sup>3</sup> of anhydrous acetonitrile. The mixture is stirred for 17 hours at a temperature close to 20EC and then 0.038 g of sodium cyanoborohydride and 0.13 cm<sup>3</sup> of acetic acid are added under an argon atmosphere. The mixture is stirred for 3 hours at a temperature close to 20EC before a further addition of 0.1 cm<sup>3</sup> of acetic acid. The reaction mixture is again stirred for 7 hours at a temperature close to 20EC. 0.9 g of paraformaldehyde is then added and the medium is kept stirred for 17 hours at a temperature close to 20EC. The white suspension obtained is filtered and the filtrate concentrated to dryness under reduced pressure (2.7 kPa) at a temperature close to 30EC. The residual thick oil is then taken up in 15 cm<sup>3</sup> of ethyl acetate and in 3 cm<sup>3</sup> of water. After stirring for 15 minutes, the pH of the solution obtained is adjusted first to 9 by addition of concentrated sodium hydroxide, and then to 11 by addition of 1.5 cm<sup>3</sup> of 1 N sodium hydroxide. The mixture obtained is stirred for about one hour, separated after settling and the organic phase washed with twice 1 cm<sup>3</sup> of water and then extracted three times with 1 N hydrochloric acid (10 cm<sup>3</sup>, 1 cm<sup>3</sup> and 0.5 cm<sup>3</sup> successively). The pooled acidic

aqueous phases are washed with 3 cm<sup>3</sup> of ether and then alkalinized to pH 10-11 by addition of concentrated sodium hydroxide. The aqueous phase obtained is extracted with twice 4 cm<sup>3</sup> of dichloromethane and the 5 organic phases are combined, washed with 2 cm<sup>3</sup> of water, dried over magnesium sulphate, filtered on sintered glass and then concentrated to dryness under reduced pressure (2.7 kPa) at a temperature close to 30EC to give a white solid. The latter is stirred in 5 cm<sup>3</sup> of 10 ether and then filtered and dried to constant weight (90 Pa at 20EC) to give 0.17 g of a white powder. The latter is purified by flash chromatography [eluent: dichloromethane-methanol-acetonitrile (92-4-4) to give 0.067 g of (16R)-16-dimethylamino-16-deoxypristinamycin 15 II<sub>F</sub> in the form of a white solid melting at 132EC.

<sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>, δ in ppm): from 0.90 to 1.00 (mt, 6H : CH<sub>3</sub> at position 30 and CH<sub>3</sub> of ethyl at position 29) ; 1.07 (d, J = 6.5 Hz, 3H : CH<sub>3</sub> at position 20 32) ; 1.18 and 1.50 (2 mts, 1H each : CH<sub>2</sub> of ethyl at position 29) ; from 1.60 to 2.00 (mt, 6H : CH<sub>2</sub> at position 15 - CH<sub>2</sub> at position 25 - 1H of CH<sub>2</sub> at position 26 and CH at position 29) ; 1.78 (s, 3H : CH<sub>3</sub> at position 33) ; 2.12 (mt, 1H : 1H of CH<sub>2</sub> at position 26) ; 25 2.37 (s, 6H : N(CH<sub>3</sub>)<sub>2</sub>) ; 2.62 and 2.99 (2 dd, respectively J = 16 and 10 Hz and J = 16 and 4 Hz, 1H each : CH<sub>2</sub> at position 17) ; 2.76 (mt, 1H : CH at position 4) ; 3.22 (mt, 1H : CH at position 16) ; 3.51

(mt, 1H : 1H of CH<sub>2</sub> at position 9) ; 3.83 and 3.94  
(2 mts, 1H each : CH<sub>2</sub> at position 24) ; 4.35 (mt, 1H :  
1H of CH<sub>2</sub> at position 9) ; 4.67 (mt, 1H : CH at position  
14) ; 4.75 (dd, J = 9 and 2.5 Hz, 1H : CH at position  
5 27) ; 4.91 (dd, J = 9.5 and 1.5 Hz, 1H : CH at position  
3) ; 5.35 (d, J = 9 Hz, 1H : CH at position 13) ; 5.66  
(mt, 1H : CH at position 10) ; 5.80 (dd, J = 16 and  
1.5 Hz, 1H : CH at position 6) ; 6.02 (mt, 1H : CONH) ;  
10 6.18 (d, J = 16 Hz, 1H : CH at position 11) ; 6.54 (dd,  
J = 16 and 5 Hz, 1H : CH at position 5) ; 8.07 (s, 1H :  
CH at position 20).

Example 24

By carrying out the procedure in a manner  
analogous to the examples above, the following products  
15 are also prepared:

- (16R)-16-(methoxy)(methyl)amino-16-deoxopristinamycin II<sub>B</sub>
- (16R)-16-(methoxy)(methyl)amino-16-deoxopristinamycin II<sub>A</sub>
- 20 - (16R)-16-(ethoxy)(methyl)amino-16-deoxopristinamycin II<sub>B</sub>
- (16R)-16-(ethoxy)(methyl)amino-16-deoxopristinamycin II<sub>A</sub>
- (16R)-16-(methyl)(propoxyl)amino-16-deoxopristinamycin II<sub>B</sub>
- 25 - (16R)-16-(methyl)(propoxyl)amino-16-deoxopristinamycin II<sub>A</sub>
- (16R)-16-(allyloxy)(methyl)amino-16-

- deoxopristinamycin II<sub>B</sub>
- (16R)-16-(allyloxy) (methyl)amino-16-
- deoxopristinamycin II<sub>A</sub>
- (16R)-16-(cyclopropyl) (methyl)amino-16-
- 5 deoxopristinamycin II<sub>B</sub>
- (16R)-16-(cyclopropyl) (methyl)amino-16-
- deoxopristinamycin II<sub>A</sub>
- (16R)-16-(methyl) (propyn-2-yl)amino-16-
- deoxopristinamycin II<sub>B</sub>
- 10 - (16R)-16-(methyl) (propyn-2-yl)amino-16-
- deoxopristinamycin II<sub>A</sub>
- (16R)-16-(methyl) (1-pyrrolidinyl)amino-16-
- deoxopristinamycin II<sub>B</sub>

The present invention also relates to the  
15 pharmaceutical compositions containing at least one  
streptogramin derivative according to the invention, in  
the pure state, combined with a group B streptogramin  
derivative, where appropriate in salt form, and/or in  
the form of a combination with one or more compatible  
20 and pharmaceutically acceptable diluents or adjuvants.

The compositions according to the invention  
may be used by the oral, parenteral, topical or rectal  
route or in the form of aerosols.

As solid compositions for oral  
25 administration, tablets, pills, gelatin capsules,  
powders or granules may be used. In these compositions,  
the active product according to the invention,  
generally in the form of a combination, is mixed with

one or more inert diluents or adjuvants, such as sucrose, lactose or starch. These compositions may comprise substances other than diluents, for example a lubricant such as magnesium stearate or a coating

5 intended for a controlled release.

As liquid compositions for oral administration, there may be used solutions which are pharmaceutically acceptable, suspensions, emulsions, syrups and elixirs containing inert diluents such as

10 water or paraffin oil. These compositions may also comprise substances other than diluents, for example wetting, sweetening or flavouring products.

Compositions for parenteral administration may be emulsions or sterile solutions. As solvent or

15 vehicle, there may be used propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, or injectable organic esters, for example ethyl oleate. These compositions may also contain adjuvants, in particular wetting, isotonizing,

20 emulsifying, dispersing and stabilizing agents.

Sterilization may be carried out in several ways, for example with the aid of a bacteriological filter, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions

25 which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

Compositions for topical administration may be, for example, creams, ointments, lotions or

aerosols.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active ingredient, excipients such as 5 cocoa butter, semisynthetic glycerides or polyethylene glycols.

The compositions may also be aerosols. For use in the form of liquid aerosols, the compositions may be stable sterile solutions or solid compositions 10 which are dissolved at the time of use in apyrogenic sterile water, in saline or any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be directly inhaled, the active ingredient is finely divided and combined with a water-soluble 15 solid diluent or vehicle with a particle size distribution of 30 to 80  $\mu\text{m}$ , for example dextran, mannitol or lactose.

In human therapy, the new streptogramin derivatives according to the invention are particularly 20 useful in the treatment of infections of bacterial origin. The doses depend on the desired effect and the duration of treatment. The doctor will determine the dosage which he judges to be the most appropriate depending on the treatment, depending on the age, 25 weight and degree of infection and other factors specific to the subject to be treated. Generally, the doses are between 1 and 3 g of active product in 2 or 3 doses per day orally for an adult.

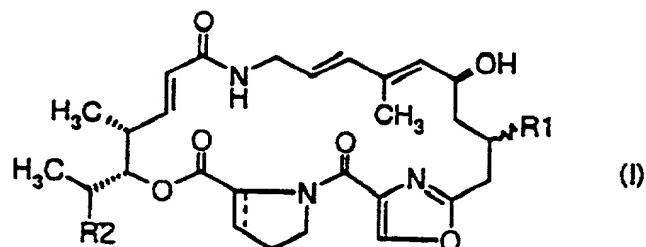
The following example illustrates a composition according to the invention.

EXAMPLE

5	Tablets containing a dose of 250 mg of active ingredient and having the following composition are prepared according to the usual technique:	
	- (16R)-16-dimethylamino-16-deoxo-	
	pristinamycin II <sub>A</sub> .....	175 mg
	- pristinamycin I <sub>B</sub> .....	75 mg
10	- excipient: starch, hydrated silica, dextrin, gelatin, magnesium stearate: qs.....	500 mg

CLAIMS

1. Derivative of group A streptogramins, characterized in that it corresponds to the general formula:



5

in which

R<sub>1</sub> is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl, benzyl or -OR''' radical, R''' being a hydrogen atom or an alkyl, cycloalkyl, allyl, propynyl or benzyl radical, or R'' represents -NR<sub>3</sub>R<sub>4</sub>, it being possible for R<sub>3</sub> and R<sub>4</sub> to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur,

R<sub>2</sub> is a hydrogen atom or a methyl or ethyl radical, and

the bond --- represents a single bond or a double bond,

- and in which unless otherwise stated, the alkyl radicals are straight or branched and contain 1 to 6 carbon atoms; the cycloalkyl radicals contain 3 to 4 carbon atoms; the chain ~~—~~ at the 16-position means:
- 5 when R'' is other than -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R and S epimers and mixtures thereof,  
as well as its salts.
- 10 2. Derivative of group A streptogramins according to claim 1, characterized in that R<sub>1</sub> is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl, cycloalkyl, allyl, propynyl, benzyl or -OR''' radical,  
15 R''' being an alkyl radical containing 1 to 6 carbon atoms, an allyl or propynyl radical, or R'' represents -NR<sub>3</sub>R<sub>4</sub>, it being possible for R<sub>3</sub> and R<sub>4</sub> to represent a methyl radical, or to form together with the nitrogen atom to which they are attached a saturated or  
20 unsaturated 4- or 5-membered heterocycle which may, in addition, contain another heteroatom chosen from nitrogen, oxygen or sulphur, R<sub>2</sub> is a hydrogen atom or a methyl or ethyl radical, and the bond — represents a single bond or a double bond, as well as their salts  
25 and in which the chain ~~—~~ at the 16-position means:  
when R'' is other than -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R epimer or mixtures of the R and S epimers in which the R epimer

is predominant, and when R'' is -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R and S epimers and mixtures thereof.

3. Derivative of group A streptogramins according to claim 1 or 2, characterized in that R<sub>1</sub> is a radical -NR'R'' for which R' is a hydrogen atom or a methyl radical, and R'' is a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, a cycloalkyl, allyl, propynyl, benzyl or -OR''' radical, R''' being an alkyl radical containing 1 to 3 carbon atoms, or an allyl or propynyl radical, or R'' represents -NR<sub>3</sub>R<sub>4</sub>, it being possible for R<sub>3</sub> and R<sub>4</sub> to form together with the nitrogen atom to which they are attached a 5-membered saturated heterocycle, R<sub>2</sub> is a methyl or ethyl radical, and the bond --- represents a single bond or a double bond, as well as their salts and in which the chain ~~-----~~ at the 16-position means: when R'' is other than -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R epimer or mixtures of the R and S epimers in which the R epimer is predominant, and when R'' is -OR''' or -NR<sub>3</sub>R<sub>4</sub>, the R and S epimers and mixtures thereof.

4. Derivative of group A streptogramins according to claim 1, characterized in that it is (16R)-16-dimethylamino-16-deoxopristinamycin II<sub>A</sub> as well as its salts.

25 5. Derivative of group A streptogramins according to claim 1, characterized in that it is (16R)-16-methoxyamino-16-deoxopristinamycin II<sub>B</sub> as well as its salts.

6. Derivative of group A streptogramins according to claim 1, characterized in that it is (16R)-16-ethoxyamino-16-deoxopristinamycin II<sub>B</sub> as well as its salts.

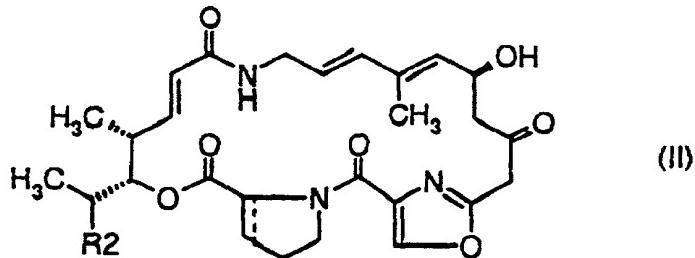
5 7. Derivative of group A streptogramins according to claim 1, characterized in that it is (16R)-16-allyloxyamino-16-deoxopristinamycin II<sub>B</sub> as well as its salts.

10 8. Derivative of group A streptogramins according to claim 1, characterized in that it is (16R)-16-methoxyamino-16-deoxopristinamycin II<sub>A</sub> as well as its salts.

15 9. Process for preparing a streptogramin derivative according to claim 1, characterized in that an amine of general formula:



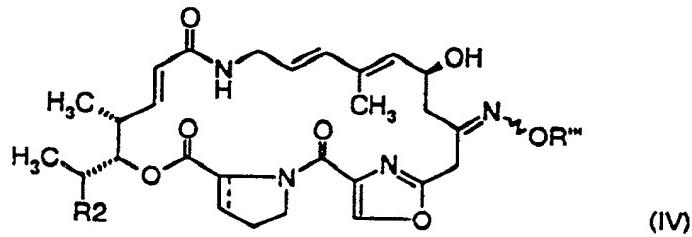
in which R'' is as defined above, is reacted with a component of natural pristinamycin of general formula:



20 in which R<sub>2</sub> is as defined in claim 1, and then an agent for reducing the intermediate enamine (or oxime) obtained is caused to react and, when it is desired to obtain a streptogramin derivative according to claim 1

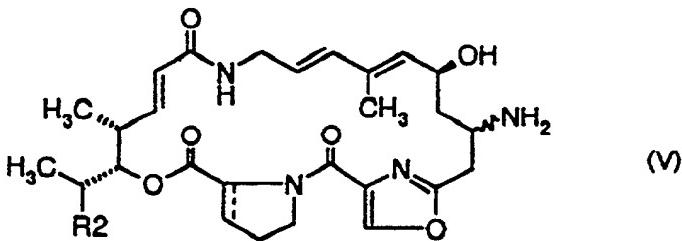
for which R' is a methyl radical, a second reductive amination is carried out by the action of formaldehyde or of a derivative generating formaldehyde in situ, followed by the reduction of the intermediate enamine, 5 the product obtained is optionally converted to a salt, and/or its R epimer is separated.

10. Process according to claim 9, characterized in that to prepare a streptogramin derivative according to claim 1 for which R'' is a 10 radical -OR''', the intermediate oxime of general formula:



in which R<sub>2</sub> and R''' are as defined in claim 1, is 15 isolated, and then converted by reduction to a streptogramin derivative according to claim 1 for which R' is a hydrogen atom, which may be optionally used in the subsequent reductive amination operation.

20. Process for preparing a streptogramin derivative according to claim 1, characterized in that the ketone corresponding to the desired R'' radical is reacted with the amine-containing derivative of general formula:



in which  $R_2$  is as defined above, and then when it is  
desired to obtain a streptogramin derivative according  
5 to claim 1, for which  $R'$  is a methyl radical, a second  
reductive amination is carried out, by the action of  
formaldehyde or of a derivative generating formaldehyde  
in situ and the intermediate enamine is reduced, and  
the product obtained is optionally converted to a salt,  
10 and/or its  $R$  epimer is separated.

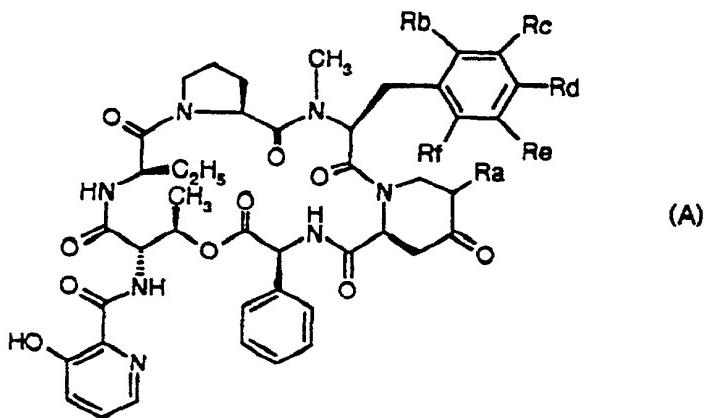
12. Combinations characterized in that they comprise a group A streptogramin derivative according to claim 1 and a group B streptogramin derivative.

13. Combinations according to claim 12,  
15 characterized in that the group B streptogramin derivative is chosen from natural components or semisynthetic components.

14. Combinations according to claim 12,  
characterized in that the group B streptogramin  
20 derivative is chosen from pristinamycin  $I_A$ , pristinamycin  $I_B$ , pristinamycin  $I_C$ , pristinamycin  $I_D$ , pristinamycin  $I_E$ , pristinamycin  $I_F$ , pristinamycin  $I_G$ , virginiamycin  $S_1$ ,  $S_3$  or  $S_4$ , vernamycin B or C or etamycin.

15. Combinations according to claim 12,  
 characterized in that the group B streptogramin  
 derivative is chosen from the streptogramin derivatives  
 of general formula:

5



in which,

1. Rb, Rc, Re and Rf are hydrogen atoms, Rd is a hydrogen atom or a dimethylamino radical, and Ra is a radical of structure  $-\text{CH}_2\text{R}'\text{a}$  for which R'a is 3-pyrrolidinylthio or 3- or 4-piperidylthio which may be substituted with alkyl, or alkylthio substituted with 1 or 2 hydroxysulphonyl, alkylamino, dialkylamino (itself optionally substituted with mercapto or dialkylamino), or substituted with 1 or 2 optionally substituted piperazine rings, morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or 3-pyrrolidinyl (which may be substituted with alkyl), or alternatively Ra is a radical of structure  $=\text{CHR}'\text{a}$  for which R'a is

- 3-pyrrolidinylamino, 3- or 4-piperidylamino,  
3-pyrrolidinyloxy, 3- or 4-piperidyloxy,  
3-pyrrolidinylthio, 3- or 4-piperidylthio which  
may be substituted with alkyl, or R'a is  
5 alkylamino, alkyloxy or alkylthio substituted with  
1 or 2 hydroxysulphonyl, alkylamino, dialkylamino  
(itself optionally substituted with dialkylamino),  
or with trialkylammonio, 4- or 5-imidazolyl, or  
with 1 or 2 optionally substituted piperazine  
10 rings, morpholino, thiomorpholino, piperidino,  
1-pyrrolidinyl, 2-, 3- or 4-piperidyl or 2- or  
3-pyrrolidinyl (which may be substituted with  
alkyl), or  
Ra is a 3- or 4-quinuclidinylthiomethyl radical,  
15 or alternatively  
2. Ra is a hydrogen atom and  
  
a) either Rb, Re and Rf are hydrogen atoms, Rd is a  
radical -NHCH<sub>3</sub> or -N(CH<sub>3</sub>)<sub>2</sub> and Rc is a chlorine or  
20 bromine atom, or represents an alkenyl radical  
containing 3 to 5 carbon atoms [if Rd is -N(CH<sub>3</sub>)<sub>2</sub>],  
  
b) or Rb, Rd, Re and Rf represent a hydrogen atom and  
Rc is a halogen, or an aminomonooalkyl,  
25 aminodialkyl, alkyloxy, trifluoromethoxy,  
thioalkyl, C<sub>1</sub> to C<sub>3</sub> alkyl or trihalomethyl radical,  
  
c) or Rb, Rc, Re and Rf represent a hydrogen atom and

Rd is a halogen, or an ethylamino, diethylamino or methylethylamino, alkyloxy or trifluoromethyloxy, thioalkyl, C<sub>1</sub> to C<sub>6</sub> alkyl, aryl or trihalomethyl radical,

5

- d) or Rb, Re and Rf represent a hydrogen atom and Rc is halogen or an aminomonooalkyl or aminodialkyl, alkyloxy or trifluoromethyloxy, thioalkyl or C<sub>1</sub> to C<sub>3</sub> alkyl radical, and Rd is halogen or an amino, aminomonooalkyl or aminodialkyl, alkyloxy or trifluoromethyloxy, thioalkyl, C<sub>1</sub> to C<sub>6</sub> alkyl or trihalomethyl radical,
- e) or Rc, Re and Rf represent a hydrogen atom and Rb and Rd represent a methyl radical.

16. Pharmaceutical composition,  
characterized in that it contains at least one streptogramin derivative according to one of claims 1 to 8, optionally in combination with a group B  
20 streptogramin derivative, and/or optionally in combination with any compatible and pharmaceutically acceptable diluent or adjuvant.